

REFERENCE

NO.

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**In re application of: Hong Liu et al.
Application No.: not yet assigned
Filing Date: March 23, 2004
Attorney Docket No.: 021288-002710US**



PCT

WORLD INTELLECTUAL PROPERTY ORGANIZATION
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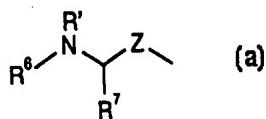
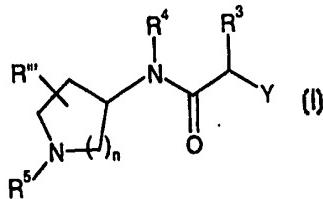
INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification 6 : C12N 9/99, 9/48, 9/66, 9/50, A61K 38/00, 38/06, A01N 37/18, 43/40, 43/42, 43/36, C07D 207/00, 207/04, 207/06, 211/00, 211/08, 405/00		A1	(11) International Publication Number: WO 98/50534 (43) International Publication Date: 12 November 1998 (12.11.98)
(21) International Application Number: PCT/US98/09192 (22) International Filing Date: 6 May 1998 (06.05.98)		(81) Designated States: AL, AU, BA, BB, BG, BR, CA, CN, CZ, EE, GE, HU, ID, IL, IS, JP, KP, KR, LC, LK, LR, LT, LV, MG, MK, MN, MX, NO, NZ, PL, RO, SG, SI, SK, SL, TR, TT, UA, US, UZ, VN, YU, ARIPO patent (GH, GM, KE, LS, MW, SD, SZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TI, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG).	
(30) Priority Data: 60/046,865 8 May 1997 (08.05.97) US		Published With international search report.	
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(54) Title: PROTEASE INHIBITORS

(57) Abstract

This invention relates to compounds of formula (I) wherein: Y is Ar or NR¹R²; R¹ is R'', R''C(O), R''C(S), R''SO₂, R''OC(O), R''R'NC(O), or R''R'NC(S); R² is H, C₁-6alkyl, C₂-6alkenyl, Ar-C₀-6alkyl, or Het-C₀-6alkyl; R³ is H, C₂-6alkenyl, C₂-6alkynyl, Het, Ar or C₁-6alkyl optionally substituted by OR', SR', NR'₂, N(R')C(O)OR'', CO₂R', CO₂NR'₂, N(C=NH)NH₂, Het by OR', SR', NR'₂, N(R')C(O)OR'', CO₂R', CO₂NR'₂, N(C=NH)NH₂, Het or Ar; R⁴ is H, C₁-6alkenyl, C₂-6alkenyl, Ar-C₀-6alkyl, or Het-C₀-6alkyl; R⁵ or Ar; R⁴ is H, C₁-6alkyl, C₂-6alkenyl, Het-C₀-6alkyl, adamantly-C(O)-, Ar-C(O)-, Het-C(O)-; is (a), Ar-C₀-6alkyl, Het-C₀-6alkyl, adamantly-C(O)-, Ar-C(O)-, Het-C(O)-; R⁶ is R'', R''C(O), R''C(S), R''SO₂, R''OC(O), R''R'NC(O), R''R'NC(S), or R''OC(O)NR'CH(R*)C(O); R⁷ is C₃-6cycloalkyl-C₀-6alkyl, Ar-C₀-6alkyl, Het-C₀-6alkyl, Ar-C₀-6alkoxy, Het-C₀-6alkoxy, or C₁-6alkyl optionally substituted by OR', SR', NR'₂, N(R')C(O)OR'', CO₂R', CO₂NR'₂, N(C=NH)NH₂, Het or Ar; R⁸ is H, C₁-6alkyl, C₂-6alkenyl, C₃-6cycloalkyl-C₀-6alkyl, Ar-C₀-6alkyl, Het-C₀-6alkyl; each R' independently is H, C₁-6alkyl, C₂-6alkenyl, Ar-C₀-6alkyl, or Het-C₀-6alkyl; each R'' independently is C₁-6alkyl, C₃-6cycloalkyl-C₀-6alkyl, Ar-C₀-6alkyl, or Het-C₀-6alkyl; R''' is H, C₁-6alkyl, C₃-6cycloalkyl-C₀-6alkyl, Ar-C₀-6alkyl, or Het-C₀-6alkyl; Z is C(O) or CH₂; and is 1, 2 or 3; or a pharmaceutically acceptable salt thereof, which are inhibitors of cysteine proteases, particularly cathepsin K, and are useful in the treatment of diseases in which inhibition of bone loss is a factor.



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PROTEASE INHIBITORSField of the Invention

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This invention relates to novel protease inhibitors, particularly inhibitors of cysteine and serine proteases, more particularly compounds which inhibit cysteine proteases, even more particularly compounds which inhibit cysteine proteases of the papain superfamily, yet more particularly compounds which inhibit cysteine proteases of the cathepsin family, most particularly compounds which inhibit cathepsin K. Such compounds are particularly useful for treating diseases in which cysteine proteases are implicated, especially diseases of excessive bone or cartilage loss, e.g., osteoporosis, periodontitis, and arthritis.

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Background of the Invention

Cathepsin K is a member of the family of enzymes which are part of the papain superfamily of cysteine proteases. Cathepsins B, H, L, N and S have been described in the literature. Recently, cathepsin K polypeptide and the cDNA encoding such polypeptide were disclosed in U.S. Patent No. 5,501,969 (called cathepsin O therein). Cathepsin K has been recently expressed, purified, and characterized. Bossard, M. J., et al., (1996) *J. Biol. Chem.* 271, 12517-12524; Drake, F.H., et al., (1996) *J. Biol. Chem.* 271, 12511-12516; Bromme, D., et al., (1996) *J. Biol. Chem.* 271, 2126-2132.

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Cathepsin K has been variously denoted as cathepsin O, cathepsin X or cathepsin O2 in the literature. The designation cathepsin K is considered to be the more appropriate one (name assigned by Nomenclature Committee of the International Union of Biochemistry and Molecular Biology).

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Cathepsins of the papain superfamily of cysteine proteases function in the normal physiological process of protein degradation in animals, including humans, e.g., in the degradation of connective tissue. However, elevated levels of these enzymes in the body can result in pathological conditions leading to disease. Thus, cathepsins have been implicated in various disease states, including but not limited to, infections by pneumocystis carinii, trypanoma cruzi, trypanoma brucei, and Crithidia fusiculata; as well as in schistosomiasis malaria, tumor metastasis, metachromatic leukodystrophy, muscular dystrophy, amyotrophy, and the like. See International Publication Number WO 94/04172, published on March 3, 1994, and references cited therein. See also European Patent Application EP 0 603 873 A1, and references cited

therein. Two bacterial cysteine proteases from *P. gingivallis*, called gingipains, have been implicated in the pathogenesis of gingivitis. Potempa, J., et al. (1994) *Perspectives in Drug Discovery and Design*, 2, 445-458.

Cathepsin K is believed to play a causative role in diseases of excessive bone or cartilage loss. Bone is composed of a protein matrix in which spindle- or plate-shaped crystals of hydroxyapatite are incorporated. Type I Collagen represents the major structural protein of bone comprising approximately 90% of the structural protein. The remaining 10% of matrix is composed of a number of non-collagenous proteins, including osteocalcin, proteoglycans, osteopontin, osteonectin, thrombospondin, fibronectin, and bone sialoprotein. Skeletal bone undergoes remodeling at discrete foci throughout life. These foci, or remodeling units, undergo a cycle consisting of a bone resorption phase followed by a phase of bone replacement.

Bone resorption is carried out by osteoclasts, which are multinuclear cells of hematopoietic lineage. The osteoclasts adhere to the bone surface and form a tight sealing zone, followed by extensive membrane ruffling on their apical (i.e., resorbing) surface. This creates an enclosed extracellular compartment on the bone surface that is acidified by proton pumps in the ruffled membrane, and into which the osteoclast secretes proteolytic enzymes. The low pH of the compartment dissolves hydroxyapatite crystals at the bone surface, while the proteolytic enzymes digest the protein matrix. In this way, a resorption lacuna, or pit, is formed. At the end of this phase of the cycle, osteoblasts lay down a new protein matrix that is subsequently mineralized. In several disease states, such as osteoporosis and Paget's disease, the normal balance between bone resorption and formation is disrupted, and there is a net loss of bone at each cycle. Ultimately, this leads to weakening of the bone and may result in increased fracture risk with minimal trauma.

The abundant selective expression of cathepsin K in osteoclasts strongly suggests that this enzyme is essential for bone resorption. Thus, selective inhibition of cathepsin K may provide an effective treatment for diseases of excessive bone loss, including, but not limited to, osteoporosis, gingival diseases such as gingivitis and periodontitis, Paget's disease, hypercalcemia of malignancy, and metabolic bone disease. Cathepsin K levels have also been demonstrated to be elevated in chondroclasts of osteoarthritic synovium. Thus, selective inhibition of cathepsin K may also be useful for treating diseases of excessive cartilage or matrix degradation, including, but not limited to, osteoarthritis and rheumatoid arthritis. Metastatic neoplastic cells also typically express high levels of proteolytic enzymes that degrade the surrounding matrix. Thus, selective inhibition of cathepsin K may also be useful for treating certain neoplastic diseases.

It now has been discovered that a novel class of compounds are protease inhibitors, most particularly inhibitors of cathepsin K, and these compounds are useful for treating diseases in which inhibition of bone resorption is indicated, such as osteoporosis and periodontal disease.

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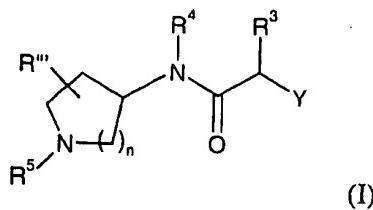
Summary of the Invention

- An object of the present invention is to provide protease inhibitors, particularly such inhibitors of cysteine and serine proteases, more particularly such compounds which inhibit cysteine proteases, even more particularly such compounds which inhibit cysteine proteases of the papain superfamily, yet more particularly such compounds which inhibit cysteine proteases of the cathepsin family, most particularly such compounds which inhibit cathepsin K, and which are useful for treating diseases which may be therapeutically modified by altering the activity of such proteases.
- 10 Accordingly, in the first aspect, this invention provides a compound according to formula (I).
- In another aspect, this invention provides a pharmaceutical composition comprising a compound according to formula (I) and a pharmaceutically acceptable carrier.
- 15 In yet another aspect, this invention provides a method of treating diseases in which the disease pathology may be therapeutically modified by inhibiting proteases, particularly cysteine and serine proteases, more particularly cysteine proteases, even more particularly cysteine proteases of the papain superfamily, yet more particularly cysteine proteases of the cathepsin family, most particularly cathepsin K.
- 20 In a particular aspect, the compounds of this invention are especially useful for treating diseases characterized by bone loss, such as osteoporosis and gingival diseases, such as gingivitis and periodontitis, or by excessive cartilage or matrix degradation, such as osteoarthritis and rheumatoid arthritis.

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Detailed Description of the Invention

The present invention provides compounds of formula (I):



wherein:

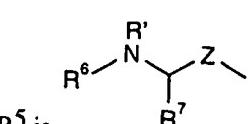
Y is Ar or NR¹R²;

5 R¹ is R'', R''C(O), R''C(S), R''SO₂, R''OC(O), R''R'NC(O), or R''R'NC(S);

R² is H, C₁₋₆alkyl, C₂₋₆alkenyl, Ar-C₀₋₆alkyl, or Het-C₀₋₆alkyl;

10 R³ is H, C₂₋₆alkenyl, C₂₋₆alkynyl, Het, Ar or C₁₋₆alkyl optionally substituted by OR', SR', NR'₂, N(R')C(O)OR'', CO₂R', CO₂NR'₂, N(C=NH)NH₂, Het or Ar;

R⁴ is H, C₁₋₆alkyl, C₂₋₆alkenyl, Ar-C₀₋₆alkyl, or Het-C₀₋₆alkyl;



15 R⁵ is , Ar-C₀₋₆alkyl, Het-C₀₋₆alkyl, adamantlyl-C(O)-, Ar-C(O)-, or Het-C(O)-;

R⁶ is R'', R''C(O), R''C(S), R''SO₂, R''OC(O), R''R'NC(O), R''R'NC(S), or R''OC(O)NR'CH(R^{*})C(O);

20 R⁷ is C₃₋₆cycloalkyl-C₀₋₆alkyl, Ar-C₀₋₆alkyl, Het-C₀₋₆alkyl, Ar-C₀₋₆alkoxy, Het-C₀₋₆alkoxy, or C₁₋₆alkyl optionally substituted by OR', SR', NR'₂, N(R')C(O)OR'', CO₂R', CO₂NR'₂, N(C=NH)NH₂, Het or Ar;

R^{*} is H, C₁₋₆alkyl, C₂₋₆alkenyl, C₃₋₆cycloalkyl-C₀₋₆alkyl, Ar-C₀₋₆alkyl, Het-C₀₋₆alkyl;

25 each R' independently is H, C₁₋₆alkyl, C₂₋₆alkenyl, Ar-C₀₋₆alkyl, or Het-C₀₋₆alkyl;

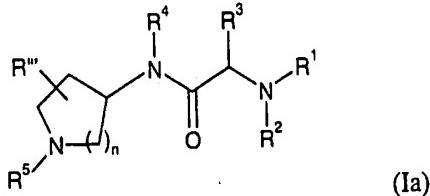
each R'' independently is C₁₋₆alkyl, C₃₋₆cycloalkyl-C₀₋₆alkyl, Ar-C₀₋₆alkyl, or Het-C₀₋₆alkyl;

R''' is H, C₁₋₆alkyl, C₃₋₆cycloalkyl-C₀₋₆alkyl, Ar-C₀₋₆alkyl, or Het-C₀₋₆alkyl; Z is C(O) or CH₂; and

n is 1, 2 or 3;

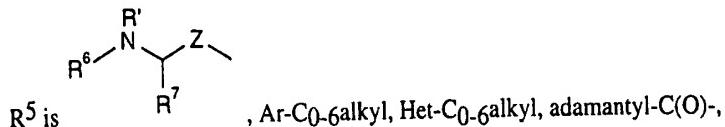
or a pharmaceutically acceptable salt thereof.

Preferably, the present invention provides compounds of formula (Ia):



wherein:

- R^1 is $R''C(O)$, $R''C(S)$, $R''SO_2$, $R''OC(O)$, $R''R'NC(O)$, or $R''R'NC(S)$;
- R^2 is H, C_{1-6} alkyl, C_{2-6} alkenyl, Ar-C $0-6$ alkyl, or Het-C $0-6$ alkyl;
- 5 R^3 is H, C_{2-6} alkenyl, C_{2-6} alkynyl, Het, Ar or C_{1-6} alkyl optionally substituted by OR', SR', NR'2, N(R')C(O)OR'', CO₂R', CO₂NR'2, N(C=NH)NH₂, Het or Ar;
- by OR', SR', NR'2, N(R')C(O)OR'', CO₂R', CO₂NR'2, N(C=NH)NH₂, Het or Ar;
- R^4 is H, C_{1-6} alkyl, C_{2-6} alkenyl, Ar-C $0-6$ alkyl, or Het-C $0-6$ alkyl;



- 10 Ar-C(O)-, or Het-C(O)-;
- R^6 is R'' , $R''C(O)$, $R''C(S)$, $R''SO_2$, $R''OC(O)$, $R''R'NC(O)$, $R''R'NC(S)$, or $R''OC(O)NR'CH(R^*)C(O)$;
- R^7 is C_{3-6} cycloalkyl-C $0-6$ alkyl, Ar-C $0-6$ alkyl, Het-C $0-6$ alkyl, Ar-C $0-6$ alkoxy, Het-C $0-6$ alkoxy, or C_{1-6} alkyl optionally substituted by OR', SR', NR'2, N(R')C(O)OR'', CO₂R', CO₂NR'2, N(C=NH)NH₂, Het or Ar;
- 15 R^* is H, C_{1-6} alkyl, C_{2-6} alkenyl, C_{3-6} cycloalkyl-C $0-6$ alkyl, Ar-C $0-6$ alkyl, Het-C $0-6$ alkyl;
- each R' independently is H, C_{1-6} alkyl, C_{2-6} alkenyl, Ar-C $0-6$ alkyl, or Het-C $0-6$ alkyl;
- 20 each R'' independently is C_{1-6} alkyl, C_{3-6} cycloalkyl-C $0-6$ alkyl, Ar-C $0-6$ alkyl, or Het-C $0-6$ alkyl;
- R''' is H, C_{1-6} alkyl, C_{3-6} cycloalkyl-C $0-6$ alkyl, Ar-C $0-6$ alkyl, or Het-C $0-6$ alkyl;
- Z is C(O) or CH₂; and
- n is 1, 2 or 3;
- 25 or a pharmaceutically acceptable salt thereof.

The present invention includes all hydrates, solvates, complexes and prodrugs of the compounds of this invention. Prodrugs are any covalently bonded compounds which release the active parent drug according to formula (I) *in vivo*. If a chiral center or another form of an isomeric center is present in a compound of the present invention, all forms of such isomer or isomers, including enantiomers and diastereomers, are intended to be covered herein. Inventive compounds containing a chiral center may be used as a

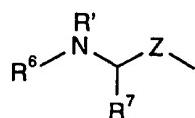
racemic mixture, an enantiomerically enriched mixture, or the racemic mixture may be separated using well-known techniques and an individual enantiomer may be used alone. In cases in which compounds have unsaturated carbon-carbon double bonds, both the cis (Z) and trans (E) isomers are within the scope of this invention. In cases 5 wherein compounds may exist in tautomeric forms, such as keto-enol tautomers, each tautomeric form is contemplated as being included within this invention whether existing in equilibrium or predominantly in one form.

The meaning of any substituent at any one occurrence in formula (I) or any 10 subformula thereof is independent of its meaning, or any other substituent's meaning, at any other occurrence, unless specified otherwise.

With respect to formula (I):

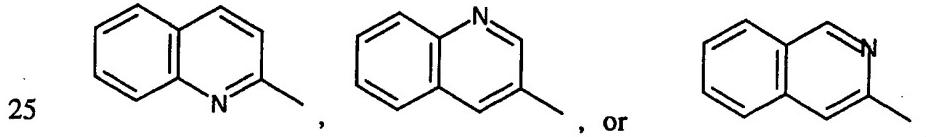
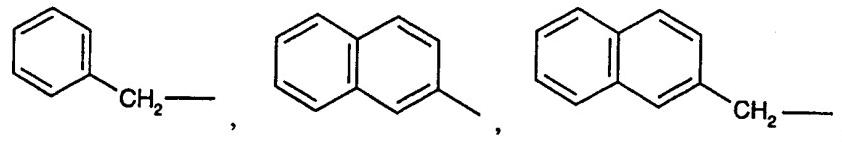
Suitably, R⁴ and R["] are each H and R³ is C₁-6alkyl or C₂-6alkenyl. Preferably, R³ is i-butyl.

15 Suitably, R⁵ is benzyl or



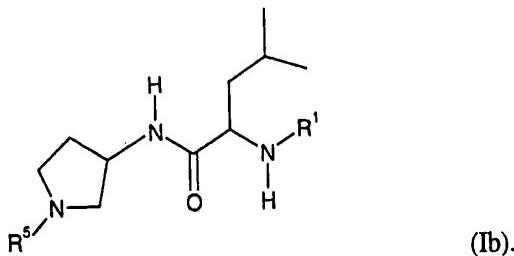
, in which R' is H, R⁷ is C₁-6alkyl, preferably i-butyl, R⁶ is R["]OC(O), wherein R" is benzyl, and Z is CH₂.

Suitably, Y is NR¹R², in which R² is H and R¹ is R["]C(O) or R["]OC(O), and R" in said 20 R¹ group is C₁-6alkyl, Ar-C₀-6alkyl or Het-C₀-6alkyl, and, most preferably, R" is tert-butyl,

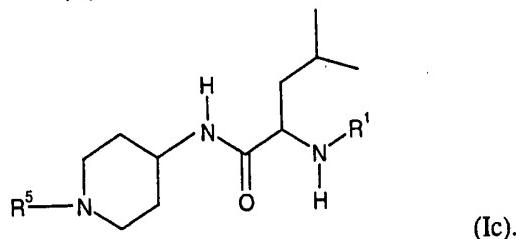


Suitably, n is 1 or 2. Preferably, n is 1.

In one particular embodiment, the formula (Ia) compound of this invention is a compound of formula (Ib):



In another embodiment, the formula (Ia) compound of this invention is a compound of formula (Ic):



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Specific representative compounds of this invention are:

- 3-[[N^α-(2-quinolinecarbonyl)-L-leucinyl]amino]-1-[(2S)-4-methyl-2-[(benzyloxycarbonyl)amino]pentyl]-pyrrolidine;
- 10 1-benzyl-3-[[N^α-(2-quinolinecarbonyl)-L-leucinyl]amino]- pyrrolidine;
- 3-[[N^α-(2-naphthylcarbonyl)-L-leucinyl]amino]-1-[(2S)-4-methyl-2-[(benzyloxycarbonyl)amino]pentyl]-pyrrolidine;
- 15 1-benzyl-3-[[N^α-(2-naphthylcarbonyl)-L-leucinyl]amino]-pyrrolidine;
- 1-benzyl-(3S)-[[N^α-(benzyloxycarbonyl)-L-leucinyl]amino]-pyrrolidine;
- 1-benzyl-(3S)-[[N^α-(tert-butoxycarbonyl)-L-leucinyl]amino]-pyrrolidine;
- 20 1-benzyl-(3S)-[[N^α-(2-naphthylcarbonyl)-L-leucinyl]amino]-1-[(2S)-4-methyl-2-[(benzyloxycarbonyl)amino]pentyl]-pyrrolidine;
- (3R)-[[N^α-(2-naphthylcarbonyl)-L-leucinyl]amino]-1-[(2S)-4-methyl-2-[(benzyloxycarbonyl)amino]pentyl]-pyrrolidine;
- 25 1-benzyl-(3R)-[[N^α-(2-naphthyl)acetyl-L-leucinyl]amino]-pyrrolidine;
- 1-benzyl-(3R)-[[N^α-(2-naphthylcarbonyl)-L-leucinyl]amino]-pyrrolidine;
- 1-benzyl-(3R)-[[N^α-(3-quinolinecarbonyl)-L-leucinyl]amino]-pyrrolidine;
- 1-benzyl-(3R)-[[N^α-(2-quinolinecarbonyl)-L-leucinyl]amino]-pyrrolidine;
- 1-benzyl-(3R)-[[N^α-(3-isoquinolinecarbonyl)-L-leucinyl]amino]-pyrrolidine;
- 1-benzyl-(3S)-[[N^α-(2-naphthyl)acetyl-L-leucinyl]amino]-pyrrolidine;
- 1-benzyl-(3S)-[[N^α-(2-naphthylcarbonyl)-L-leucinyl]amino]-pyrrolidine;
- 1-benzyl-(3S)-[[N^α-(3-quinolinecarbonyl)-L-leucinyl]amino]-pyrrolidine;

- 1-benzyl-(3S)-[[N^α-(2-quinolinecarbonyl)-L-leucinyl]amino]-pyrrolidine;
1-benzyl-(3S)-[[N^α-(3-isoquinolinecarbonyl)-L-leucinyl]amino]-pyrrolidine;
1-benzyl-4-[[N^α-(2-naphthylcarbonyl)-L-leucinyl]amino]-piperidine;
1-benzyl-4-[[N^α-(2-quinolinecarbonyl)-L-leucinyl]amino]-piperidine;
5 1-benzyl-4-[[N^α-(benzyloxycarbonyl)-L-leucinyl]amino]-piperidine;
1-[3-(2-pyridyl)phenyl]-2-ethyl-(3S)-[[N^α-(2-naphthylcarbonyl)-L-leucinyl]amino]-pyrrolidine;
1-[3-(2-pyridyl)phenyl]-2-ethyl-(3S)-[[N^α-(2-quinolinecarbonyl)-L-leucinyl]amino]-pyrrolidine;
10 1-[3-(2-pyridyl)phenyl]-2-ethyl-(3S)-[[N^α-(3-isoquinolinecarbonyl)-L-leucinyl]amino]-pyrrolidine;
1-[3-(2-pyridyl)phenyl]-2-ethyl-(3R)-[[N^α-(2-naphthylcarbonyl)-L-leucinyl]amino]-pyrrolidine;
1-[3-(2-pyridyl)phenyl]-2-ethyl-(3R)-[[N^α-(3-isoquinolinecarbonyl)-L-leucinyl]amino]-pyrrolidine;
15 1-(1-adamantanecarbonyl)-(3R)-[[N^α-(4-pyridylmethoxycarbonyl)-L-leucinyl]amino]-pyrrolidine;
1-(1-adamantanecarbonyl)-(3S)-[[N^α-(4-pyridylmethoxycarbonyl)-L-leucinyl]amino]-pyrrolidine;
1-(3R)-[[N^α-(benzo[b]thiophene-2-carbonyl)-L-leucinyl]amino]-1-[(2S)-4-methyl-2-
20 [[[benzyloxycarbonyl]amino]pentyl]-pyrrolidine;
1-(3R)-[[N^α-(3,4-dimethoxybenzoyl)-L-leucinyl]amino]-1-[(2S)-4-methyl-2-
25 [[[benzyloxycarbonyl]amino]pentyl]-pyrrolidine;
1-(3R)-[[N^α-(benzofuran-2-carbonyl)-L-leucinyl]amino]-1-[(2S)-4-methyl-2-
[[[benzyloxycarbonyl]amino]pentyl]-pyrrolidine;
1-(3R)-[[N^α-(benzothiazole-6-carbonyl)-L-leucinyl]amino]-1-[(2S)-4-methyl-2-
30 [[[benzyloxycarbonyl]amino]pentyl]-pyrrolidine;
1-(3R)-[[N^α-(indole-2-carbonyl)-L-leucinyl]amino]-1-[(2S)-4-methyl-2-
[[[benzyloxycarbonyl]amino]pentyl]-pyrrolidine;
1-(3R)-[[N^α-(4-fluorobenzoyl)-L-leucinyl]amino]-1-[(2S)-4-methyl-2-
35 [[[benzyloxycarbonyl]amino]pentyl]-pyrrolidine;
1-(3R)-[[N^α-(4-methoxybenzoyl)-L-leucinyl]amino]-1-[(2S)-4-methyl-2-
[[[benzyloxycarbonyl]amino]pentyl]-pyrrolidine;
1-(3R)-[[N^α-(3,4-dichlorobenzoyl)-L-leucinyl]amino]-1-[(2S)-4-methyl-2-
[[[benzyloxycarbonyl]amino]pentyl]-pyrrolidine;

- (3R)-[[N^α-(thiophene-2-carbonyl)-L-leucinyl]amino]-1-[(2S)-4-methyl-2-
 [[(benzyloxycarbonyl)amino]pentyl]-pyrrolidine;
- (3R)-[[N^α-(4-biphenylcarbonyl)-L-leucinyl]amino]-1-[(2S)-4-methyl-2-
 [[(benzyloxycarbonyl)amino]pentyl]-pyrrolidine;
- 5 (3R)-[[N^α-(5-methoxybenzofuran-2-carbonyl)-L-leucinyl]amino]-1-[(2S)-4-methyl-2-
 [[(benzyloxycarbonyl)amino]pentyl]-pyrrolidine;
- (3R)-[[N^α-(5-chlorobenzofuran-2-carbonyl)-L-leucinyl]amino]-1-[(2S)-4-methyl-2-
 [[(benzyloxycarbonyl)amino]pentyl]-pyrrolidine;
- 10 (3R)-[[N^α-(7-methoxybenzofuran-2-carbonyl)-L-leucinyl]amino]-1-[(2S)-4-methyl-2-
 [[(benzyloxycarbonyl)amino]pentyl]-pyrrolidine;
- (3R)-[[N^α-(3-chlorobenzo[b]thiophene-2-carbonyl)-L-leucinyl]amino]-1-[(2S)-4-methyl-2-
 2-[[(benzyloxycarbonyl)amino]pentyl]-pyrrolidine;
- (3R)-[[N^α-(3-(2-pyridyl)benzoyl)-L-leucinyl]amino]-1-[(2S)-4-methyl-2-
 [[(benzyloxycarbonyl)amino]pentyl]-pyrrolidine;
- 15 (3S)-[[N^α-(benzo[b]thiophene-2-carbonyl)-L-leucinyl]amino]-1-[(2S)-4-methyl-2-
 [[(benzyloxycarbonyl)amino]pentyl]-pyrrolidine;
- (3S)-[[N^α-(3,4-dimethoxybenzoyl)-L-leucinyl]amino]-1-[(2S)-4-methyl-2-
 [[(benzyloxycarbonyl)amino]pentyl]-pyrrolidine;
- (3S)-[[N^α-(benzofuran-2-carbonyl)-L-leucinyl]amino]-1-[(2S)-4-methyl-2-
 20 [[(benzyloxycarbonyl)amino]pentyl]-pyrrolidine;
- (3S)-[[N^α-(benzothiazole-6-carbonyl)-L-leucinyl]amino]-1-[(2S)-4-methyl-2-
 [[(benzyloxycarbonyl)amino]pentyl]-pyrrolidine;
- (3S)-[[N^α-(indole-2-carbonyl)-L-leucinyl]amino]-1-[(2S)-4-methyl-2-
 [[(benzyloxycarbonyl)amino]pentyl]-pyrrolidine;
- 25 (3S)-[[N^α-(4-fluorobenzoyl)-L-leucinyl]amino]-1-[(2S)-4-methyl-2-
 [[(benzyloxycarbonyl)amino]pentyl]-pyrrolidine;
- (3S)-[[N^α-(4-methoxybenzoyl)-L-leucinyl]amino]-1-[(2S)-4-methyl-2-
 [[(benzyloxycarbonyl)amino]pentyl]-pyrrolidine;
- (3S)-[[N^α-(3,4-dichlorobenzoyl)-L-leucinyl]amino]-1-[(2S)-4-methyl-2-
 30 [[(benzyloxycarbonyl)amino]pentyl]-pyrrolidine;
- (3S)-[[N^α-(thiophene-2-carbonyl)-L-leucinyl]amino]-1-[(2S)-4-methyl-2-
 [[(benzyloxycarbonyl)amino]pentyl]-pyrrolidine;
- (3S)-[[N^α-(4-biphenylcarbonyl)-L-leucinyl]amino]-1-[(2S)-4-methyl-2-
 [[(benzyloxycarbonyl)amino]pentyl]-pyrrolidine;
- 35 (3S)-[[N^α-(5-methoxybenzofuran-2-carbonyl)-L-leucinyl]amino]-1-[(2S)-4-methyl-2-
 [[(benzyloxycarbonyl)amino]pentyl]-pyrrolidine;

- (3S)-[[N^α-(5-chlorobenzofuran-2-carbonyl)-L-leucinyl]amino]-1-[(2S)-4-methyl-2-
[[benzyloxycarbonyl]amino]pentyl]-pyrrolidine;
- (3S)-[[N^α-(7-methoxybenzofuran-2-carbonyl)-L-leucinyl]amino]-1-[(2S)-4-methyl-2-
[[benzyloxycarbonyl]amino]pentyl]-pyrrolidine;
- 5 (3S)-[[N^α-(3-chlorobenzo[b]thiophene-2-carbonyl)-L-leucinyl]amino]-1-[(2S)-4-methyl-2-
[[benzyloxycarbonyl]amino]pentyl]-pyrrolidine;
- (3S)-[[N^α-(3-(2-pyridyl)benzoyl)-L-leucinyl]amino]-1-[(2S)-4-methyl-2-
[[benzyloxycarbonyl]amino]pentyl]-pyrrolidine;
- 10 1-(4-phenyl)benzyl-(3S)-[[N^α-(tert-butoxycarbonyl)-L-leucinyl]amino]-pyrrolidine;
- 1-(4-phenyl)benzyl-(3S)-[[N^α-(2-naphthylcarbonyl)-L-leucinyl]amino]-pyrrolidine;
- 1-(4-phenyl)benzyl-(3S)-[[N^α-(2-quinolinecarbonyl)-L-leucinyl]amino]-pyrrolidine;
- 1-(4-phenyl)benzyl-(3S)-[[N^α-(3,4-dimethoxybenzoyl)-L-leucinyl]amino]-pyrrolidine;
- 1-(4-phenyl)benzyl-(3S)-[[N^α-(benzofuran-2-carbonyl)-L-leucinyl]amino]-pyrrolidine;
- 1-(4-phenyl)benzyl-(3S)-[[N^α-(benzo[b]thiophene-2-carbonyl)-L-leucinyl]amino]-
15 pyrrolidine;
- 1-(4-phenyl)benzyl-(3S)-[[N^α-(benzyloxycarbonyl)-L-leucinyl]amino]-pyrrolidine;
- 1-(2-phenyl)ethyl-(3S)-[[N^α-(tert-butoxycarbonyl)-L-leucinyl]amino]-pyrrolidine;
- 1-(2-phenyl)ethyl-(3S)-[[N^α-(2-naphthylcarbonyl)-L-leucinyl]amino]-pyrrolidine;
- 1-(2-phenyl)ethyl-(3S)-[[N^α-(2-quinolinecarbonyl)-L-leucinyl]amino]-pyrrolidine;
- 20 1-(2-phenyl)ethyl-(3S)-[[N^α-(benzo[b]thiophene-2-carbonyl)-L-leucinyl]amino]-
pyrrolidine;
- 1-(2-phenyl)ethyl-(3S)-[[N^α-(benzofuran-2-carbonyl)-L-leucinyl]amino]-pyrrolidine;
- 1-(2-phenyl)ethyl-(3S)-[[N^α-(3-chlorobenzo[b]thiophene-2-carbonyl)-L-leucinyl]amino]-
pyrrolidine;
- 25 1-(4-phenoxy)benzyl-(3S)-[[N^α-(tert-butoxycarbonyl)-L-leucinyl]amino]-pyrrolidine;
- 1-(4-phenoxy)benzyl-(3S)-[[N^α-(2-naphthylcarbonyl)-L-leucinyl]amino]-pyrrolidine;
- 1-(4-phenoxy)benzyl-(3S)-[[N^α-(2-quinolinecarbonyl)-L-leucinyl]amino]-pyrrolidine;
- 1-(4-phenoxy)benzyl-(3S)-[[N^α-(3,4-dimethoxybenzoyl)-L-leucinyl]amino]-pyrrolidine;
- 1-(4-phenoxy)benzyl-(3S)-[[N^α-(benzofuran-2-carbonyl)-L-leucinyl]amino]-pyrrolidine
- 30 1-(4-phenoxy)benzyl-(3S)-[[N^α-(benzo[b]thiophene-2-carbonyl)-L-leucinyl]amino]-
pyrrolidine;
- 1-(4-fluoro)benzyl-(3S)-[[N^α-(tert-butoxycarbonyl)-L-leucinyl]amino]-pyrrolidine;
- 1-(4-fluoro)benzyl-(3S)-[[N^α-(2-naphthylcarbonyl)-L-leucinyl]amino]-pyrrolidine;
- 1-(4-fluoro)benzyl-(3S)-[[N^α-(benzo[b]thiophene-2-carbonyl)-L-leucinyl]amino]-
35 pyrrolidine;
- 1-(4-cyano)benzyl-(3S)-[[N^α-(tert-butoxycarbonyl)-L-leucinyl]amino]-pyrrolidine;
- 1-(4-cyano)benzyl-(3S)-[[N^α-(2-naphthylcarbonyl)-L-leucinyl]amino]-pyrrolidine;

1-benzyl-(3S)-[[N^α-(benzo[b]thiophene-2-carbonyl)-L-leucinyl]amino]-pyrrolidine;
1-benzyl-(3S)-[[N^α-(3,4-dimethoxybenzoyl)-L-leucinyl]amino]-pyrrolidine;
1-benzyl-(3S)-[[N^α-(3-(2-dimethylaminoethoxy)-4-methoxybenzoyl)-L-leucinyl]amino]-
pyrrolidine;

5 1-(4-nitro)benzyl-(3S)-[[N^α-(2-naphthylcarbonyl)-L-leucinyl]amino]-pyrrolidine;
1-(4-(N,N-dimethylamino)benzyl-(3S)-[[N^α-(2-naphthylcarbonyl)-L-leucinyl]amino]-
pyrrolidine;
1-(4-methoxy)benzyl-(3S)-[[N^α-(2-naphthylcarbonyl)-L-leucinyl]amino]-pyrrolidine;
1-(4-pyridyl)methyl-(3S)-[[N^α-(2-naphthylcarbonyl)-L-leucinyl]amino]-pyrrolidine;
10 1-(4-carboxymethyl)benzyl-(3S)-[[N^α-(2-naphthylcarbonyl)-L-leucinyl]amino]-
pyrrolidine;
1-(3,4-methylenedioxy)benzyl-(3S)-[[N^α-(2-naphthylcarbonyl)-L-leucinyl]amino]-
pyrrolidine;
1-(2-naphthyl)methyl-(3S)-[[N^α-(2-naphthylcarbonyl)-L-leucinyl]amino]-pyrrolidine;
15 1-(3-indolyl)methyl-(3S)-[[N^α-(2-naphthylcarbonyl)-L-leucinyl]amino]-pyrrolidine;
1-(2-quinolinyl)methyl-(3S)-[[N^α-(2-naphthylcarbonyl)-L-leucinyl]amino]-pyrrolidine;
1-(3-quinolinyl)methyl-(3S)-[[N^α-(2-naphthylcarbonyl)-L-leucinyl]amino]-pyrrolidine;
1-(1-naphthyl)methyl-(3S)-[[N^α-(2-naphthylcarbonyl)-L-leucinyl]amino]-pyrrolidine;
1-(4-quinolinyl)methyl-(3S)-[[N^α-(2-naphthylcarbonyl)-L-leucinyl]amino]-pyrrolidine;

20 1-(3-pyrrolyl)methyl-(3S)-[[N^α-(2-naphthylcarbonyl)-L-leucinyl]amino]-pyrrolidine;
1-(3-pyridyl)methyl-(3S)-[[N^α-(2-naphthylcarbonyl)-L-leucinyl]amino]-pyrrolidine;
1-(2-pyridyl)methyl-(3S)-[[N^α-(2-naphthylcarbonyl)-L-leucinyl]amino]-pyrrolidine;
1-(3-nitro)benzyl-(3S)-[[N^α-(2-naphthylcarbonyl)-L-leucinyl]amino]-pyrrolidine;
1-(4-acetamido)benzyl-(3S)-[[N^α-(2-naphthylcarbonyl)-L-leucinyl]amino]-pyrrolidine;

25 1-(3-cyano)benzyl-(3S)-[[N^α-(2-naphthylcarbonyl)-L-leucinyl]amino]-pyrrolidine;
1-(3-fluoro)benzyl-(3S)-[[N^α-(2-naphthylcarbonyl)-L-leucinyl]amino]-pyrrolidine;
1-(3-phenoxy)benzyl-(3S)-[[N^α-(2-naphthylcarbonyl)-L-leucinyl]amino]-pyrrolidine;
1-(4-chloro)benzyl-(3S)-[[N^α-(2-naphthylcarbonyl)-L-leucinyl]amino]-pyrrolidine;
1-(4-trifluoromethyl)benzyl-(3S)-[[N^α-(2-naphthylcarbonyl)-L-leucinyl]amino]-

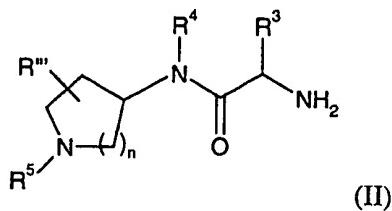
30 pyrrolidine;
1-(3-trifluoromethyl)benzyl-(3S)-[[N^α-(2-naphthylcarbonyl)-L-leucinyl]amino]-
pyrrolidine;
1-(4-(3-(N,N-dimethylamino)propoxy)benzyl-(3S)-[[N^α-(2-naphthylcarbonyl)-L-
leucinyl]amino]-pyrrolidine;

35 1-(4-(isopropyl)benzyl-(3S)-[[N^α-(2-naphthylcarbonyl)-L-leucinyl]amino]-pyrrolidine;
1-(2-benzofuranyl)methyl-(3S)-[[N^α-(2-naphthylcarbonyl)-L-leucinyl]amino]-pyrrolidine;

- 1-(2-(3-methylbenzo[b]thiophenyl)methyl-(3S)-[[N^α-(2-naphthylcarbonyl)-L-leucinyl]amino]-pyrrolidine;
- 1-(2-furanyl)methyl-(3S)-[[N^α-(2-naphthylcarbonyl)-L-leucinyl]amino]-pyrrolidine;
- 1-(3-furanyl)methyl-(3S)-[[N^α-(2-naphthylcarbonyl)-L-leucinyl]amino]-pyrrolidine;
- 5 1-(2-thiophenyl)methyl-(3S)-[[N^α-(2-naphthylcarbonyl)-L-leucinyl]amino]-pyrrolidine;
- 1-(2-nitro)benzyl-(3S)-[[N^α-(2-naphthylcarbonyl)-L-leucinyl]amino]-pyrrolidine;
- (3-thiophenyl)methyl-(3S)-[[N^α-(2-naphthylcarbonyl)-L-leucinyl]amino]-pyrrolidine;
- 1-(3,4-dimethoxy)benzyl-(3S)-[[N^α-(2-naphthylcarbonyl)-L-leucinyl]amino]-pyrrolidine;
- and
- 10 1-(5-nitro-3-furanyl)methyl-(3S)-[[N^α-(2-naphthylcarbonyl)-L-leucinyl]amino]-pyrrolidine;
- or a pharmaceutically acceptable salt thereof.

In yet another aspect, this invention provides novel intermediates useful in the preparation of formula (I) compounds represented by the formula (II):

15



wherein:

- R³ is H, C₂-6alkenyl, C₂-6alkynyl, Het, Ar or C₁-6alkyl optionally substituted by OR', SR', NR'₂, N(R')C(O)OR'', CO₂R', CO₂NR'₂, N(C=NH)NH₂, Het or Ar;
- 20 R⁴ is H, C₁-6alkyl, C₂-6alkenyl, Ar-C₀-6alkyl, or Het-C₀-6alkyl;
- R⁵ is
- , Ar-C₀-6alkyl, Het-C₀-6alkyl, adamantyl-C(O)-, Ar-C(O)-, or Het-C(O)-;
- R⁶ is R", R"C(O), R"C(S), R"SO₂, R"OC(O), R"R'NC(O), R"R'NC(S), or
- 25 R"OC(O)NR'CH(R*)C(O);
- R⁷ is C₃-6cycloalkyl-C₀-6alkyl, Ar-C₀-6alkyl, Het-C₀-6alkyl, Ar-C₀-6alkoxy, Het-C₀-6alkoxy, or C₁-6alkyl optionally substituted by OR', SR', NR'₂, N(R')C(O)OR'', CO₂R', CO₂NR'₂, N(C=NH)NH₂, Het or Ar;
- R* is H, C₁-6alkyl, C₂-6alkenyl, C₃-6cycloalkyl-C₀-6-alkyl, Ar-C₀-6alkyl,
- 30 Het-C₀-6alkyl;

each R' independently is H, C₁₋₆alkyl, C₂₋₆alkenyl, Ar-C₀₋₆alkyl, or Het-C₀₋₆alkyl;
each R" independently is C₁₋₆alkyl, C₃₋₆cycloalkyl-C₀₋₆alkyl, Ar-C₀₋₆alkyl, or Het-C₀₋₆alkyl;

5 R''' is H, C₁₋₆alkyl, C₃₋₆cycloalkyl-C₀₋₆alkyl, Ar-C₀₋₆alkyl, or Het-C₀₋₆alkyl;
Z is C(O) or CH₂; and
n is 1, 2 or 3;
or a pharmaceutically acceptable salt thereof.

Abbreviations and symbols commonly used in the peptide and chemical arts are
10 used herein to describe the compounds of the present invention. In general, the amino acid abbreviations follow the IUPAC-IUB Joint Commission on Biochemical

Nomenclature as described in *Eur. J. Biochem.*, 158, 9 (1984). The term "amino acid" as used herein refers to the D- or L- isomers of alanine, arginine, asparagine, aspartic acid, cysteine, glutamine, glutamic acid, glycine, histidine, isoleucine, leucine, lysine,

15 methionine, phenylalanine, proline, serine, threonine, tryptophan, tyrosine and valine.

"C₁₋₆alkyl" as applied herein is meant to include substituted and unsubstituted methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl and t-butyl, pentyl, n-pentyl, isopentyl, neopentyl and hexyl and the simple aliphatic isomers thereof. Any C₁₋₆alkyl group may be optionally substituted independently by one or two halogens, SR', OR',

20 N(R')₂, C(O)N(R')₂, carbamyl or C₁₋₄alkyl, where R' is H or C₁₋₆alkyl. C₀alkyl means that no alkyl group is present in the moiety. Thus, Ar-C₀alkyl is equivalent to Ar.

"C₃₋₆cycloalkyl" as applied herein is meant to include substituted and unsubstituted cyclopropane, cyclobutane, cyclopentane, and cyclohexane.

"C₂₋₆alkenyl" as applied herein means an alkyl group of 2 to 6 carbons wherein 25 a carbon-carbon single bond is replaced by a carbon-carbon double bond. C₂₋₆alkenyl includes ethylene, 1-propene, 2-propene, 1-butene, 2-butene, isobutene and the several isomeric pentenes and hexenes. Both cis and trans isomers are included.

"C₂₋₆alkynyl" means an alkyl group of 2 to 6 carbons wherein one carbon-carbon single bond is replaced by a carbon-carbon triple bond. C₂₋₆alkynyl includes 30 acetylene, 1-propyne, 2-propyne, 1-butyne, 2-butyne, 3-butyne and the simple isomers of pentyne and hexyne.

"Halogen" or "halo" means F, Cl, Br, and I.

"Ar" or "aryl" means unsubstituted phenyl or naphthyl; or phenyl or naphthyl substituted by one or more of Ph-C₀₋₆alkyl, Het-C₀₋₆alkyl, C₁₋₆alkoxy, Ph-C₀₋

35 C₀alkoxy, Het-C₀₋₆alkoxy, OH, (CH₂)₁₋₆NR'R', O(CH₂)₁₋₆NR'R'; wherein each R' independently is H, C₁₋₆alkyl, Ar-C₀₋₆alkyl, or Het-C₀₋₆alkyl; or phenyl or naphthyl substituted by one to three moieties selected from C₁₋₄alkyl, OR', N(R'), SR',

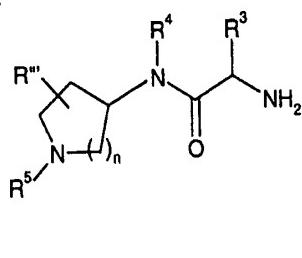
CF₃, NO₂, CN, CO₂R', CON(R'), F, Cl, Br and I, or substituted by a methylenedioxy group.

As used herein "Het" or "heterocyclic" or "heteroaryl" represents a stable 5- to 7-membered monocyclic or a stable 7- to 10-membered bicyclic heterocyclic ring,

- 5 which is either saturated or unsaturated, and which consists of carbon atoms and from one to four heteroatoms selected from the group consisting of N, O and S, and wherein the nitrogen and sulfur heteroatoms may optionally be oxidized, and the nitrogen heteroatom may optionally be quaternized, and including any bicyclic group in which any of the above-defined heterocyclic rings is fused to a benzene ring. The heterocyclic
10 ring may be attached at any heteroatom or carbon atom which results in the creation of a stable structure, and may optionally be substituted with one or two moieties selected from C₁-4alkyl, OR', N(R')₂, SR', CF₃, NO₂, CN, CO₂R', CON(R'), F, Cl, Br and I, where R' is as defined hereinbefore. Examples of such heterocycles include piperidinyl, piperazinyl, 2-oxopiperazinyl, 2-oxopiperidinyl, 2-oxopyrrolodinyl, 2-oxoazepinyl,
15 azepinyl, pyrrolyl, 4-piperidonyl, pyrrolidinyl, pyrazolyl, pyrazolidinyl, imidazolyl, pyridyl, pyrazinyl, oxazolidinyl, oxazolinyl, oxazolyl, isoxazolyl, morpholinyl, thiazolidinyl, thiazolinyl, thiazolyl, quinuclidinyl, indolyl, quinolinyl, isoquinolinyl, benzimidazolyl, benzopyranyl, benzoxazolyl, furyl, pyranyl, tetrahydrofuryl, tetrahydropyranyl, thienyl, benzoxazolyl, thiamorpholinyl sulfoxide, thiamorpholinyl
20 sulfone, oxadiazolyl, benzothiazolyl, benzoisothiazolyl, benzisoxazolyl, pyrimidinyl, cinnolinyl, quinazolinyl, quinoxaliny, 1,5-naphthyridinyl, 1,6-naphthyridinyl, 1,7-naphthyridinyl, 1,8-naphthyridinyl, tetrazolyl, 1,2,3-triazolyl, and 1,2,4-triazolyl. "Het" also means any heterocyclic moiety encompassed by the above definition of Het which is aromatic in character, e.g., pyridinyl, quinolinyl, isoquinolinyl, pyrrolyl, pyrazolyl,
25 imidazolyl, pyridyl, pyrazinyl, oxazolyl, isoxazolyl, thiazolyl, isothiazolyl, indolyl, quinolinyl, isoquinolinyl, benzimidazolyl, benzoxazolyl, furyl, thienyl, benzoxazolyl, oxadiazolyl, benzothiazolyl, benzoisothiazolyl, benzisoxazolyl, pyrimidinyl, cinnolinyl, quinazolinyl, quinoxaliny, 1,5-naphthyridinyl, 1,6-naphthyridinyl, 1,7-naphthyridinyl, 1,8-naphthyridinyl, tetrazolyl, 1,2,3-triazolyl, and 1,2,4-triazolyl.
30 Certain radical groups are abbreviated herein. t-Bu refers to the tertiary butyl radical, Boc or BOC refers to the t-butyloxycarbonyl radical, Fmoc refers to the fluorenylmethoxycarbonyl radical, Ph refers to the phenyl radical, Cbz or CBZ refers to the benzyloxycarbonyl radical.
- Certain reagents are abbreviated herein. DCC refers to
35 dicyclohexylcarbodiimide, DMAP is 2,6-dimethylaminopyridine, EDC or EDCI refers to N-ethyl-N'(dimethylaminopropyl)-carbodiimide. HOBT or HOBt refers to 1-hydroxybenzotriazole, DMF refers to dimethyl formamide, BOP refers to benzotriazol-

1-yloxy-tris(dimethylamino)phosphonium hexafluorophosphate, DMAP is dimethylaminopyridine, DIEA refers to di-isopropylethylamine, Lawesson's reagent is 2,4-bis(4-methoxyphenyl)-1,3-dithia-2,4-diphosphetane-2,4-disulfide, NMM is N-methylmorpholine, TFA refers to trifluoroacetic acid, TFAA refers to trifluoroacetic anhydride, KHMDS refers to potassium hexamethyldisilazide, and THF refers to tetrahydrofuran. Jones reagent is a solution of chromium trioxide, water, and sulfuric acid well-known in the art.

Compounds of the formula (I) are generally prepared by reacting a compound of the formula (II):



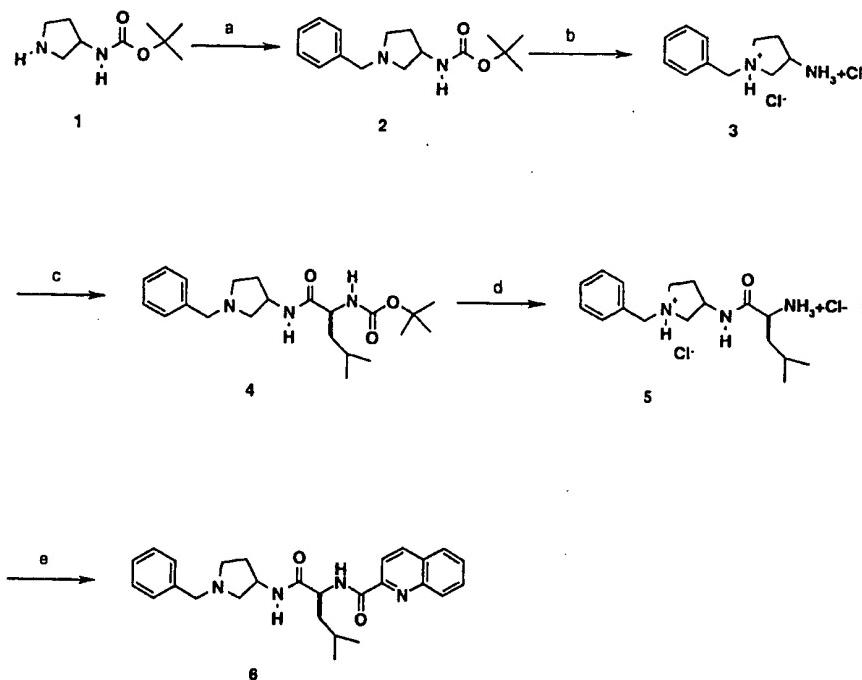
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or a salt thereof,

wherein R'', R³, R⁴, R⁵ and n are as defined in formula (I), with any reactive functional groups protected, with:

- 15 (a) R''C(O)Cl, in which R'' is as defined in formula (I) of claim 1; or
- (b) R''C(O)OH, in which R'' is as defined in formula (I) of claim 1, in the presence of EDC and HOBT; or
- (c) R''C(O)H, in which R'' is as defined in formula (I) of claim 1, followed by reduction; or
- (d) R''OC(O)Cl, in which R'' is as defined in formula (I) of claim 1, in the presence of base; or
- (e) R''SO₂Cl, in which R'' is as defined in formula (I) of claim 1, and thereafter removing any protecting groups and optionally forming a pharmaceutically acceptable salt.

Compounds of the formula (I) are prepared by methods analogous to those described in Schemes 1 and 2.

Scheme 1

- 5 a) PhCHO, CH₂Cl₂, NaBH(OAc)₃; b) HCl, EtOAc, CH₃OH; c) N-BOC-leucine, EDC, HOBr, NMM, CH₂Cl₂; d) HCl, EtOAc, CH₃OH; e) quinaldic acid, EDC, HOBr, NMM, CH₂Cl₂

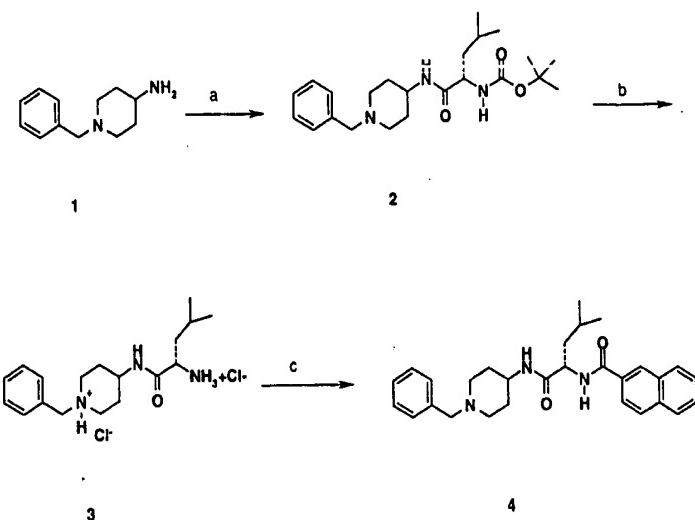
10 Compounds of the general formula (I) wherein n is 1, R⁵ is an alkyl group and R¹ is an R'C(O) can be prepared as outlined in Scheme 1. Reductive alkylation of the commercially available amine 1-Scheme-1 (this material available in racemic or enantiomerically pure form) with an aldehyde, such as benzaldehyde or CBZ-leucinal, followed by treatment with a reducing agent, such as sodium triacetoxyborohydride, affords the tertiary amine 2-Scheme-1. Removal of the protecting group by treating 2-Scheme-1 with a strong acid, such as hydrogen chloride, in ethyl acetate or ether or dioxane and methanol affords 3-Scheme-1. 3-Scheme-1 may be coupled with an acid using EDC and HOBr in the presence of a base, such as N-methylmorpholine or triethylamine, in an aprotic solvent, such as dichloromethane, to yield 4-Scheme-1. The protecting group of 4-Scheme-1 may be removed with strong acid, such as hydrogen chloride, in ethyl acetate or ether or dioxane and methanol to afford 5-Scheme-1.

15 Coupling of the amine salt 5-Scheme-1 may be effected with an acid in the presence of EDC, HOBr and a base, such as N-methylmorpholine, to yield 6-Scheme-1. The 5-

20

Scheme-1 salt may also be converted to the sulphonamide derivative by treatment with a sulphonyl chloride in the presence of a base, such as triethylamine, in an aprotic solvent, such as dichloromethane.

5

Scheme 2

a) N-BOC-leucine, EDC, HOBT, NMM, CH₂Cl₂; b) HCl, EtOAc; c) 2-naphthoic acid,
10 EDC, HOBT, CH₂Cl₂, NMM

Compounds of the general formula (I) wherein n is 2, R⁵ is a benzyl group and R¹ is an R'C(O) can be prepared as outlined in Scheme 1. Acylation of the commercially available 4-amino-1-benzylpiperidine (1-Scheme-1) with N-BOC-leucine 15 in the presence of EDC, HOBT and N-methylmorpholine in dichloromethane afforded 2-scheme-2. Removal of the protecting group with anhydrous hydrogen chloride in ethyl acetate or ether or dioxane and methanol gave 3-Scheme-2. Acylation of the amine salt 3-Scheme-2 with a carboxylic acid as described previously afforded 4-Scheme-2.

20

The starting materials used herein are commercially available amino acids or are prepared by routine methods well known to those of ordinary skill in the art and can be found in standard reference books, such as the COMPENDIUM OF ORGANIC SYNTHETIC METHODS, Vol. I-VI (published by Wiley-Interscience).

25

Coupling methods to form amide bonds herein are generally well known to the art. The methods of peptide synthesis generally set forth by Bodansky *et al.*, THE

PRACTICE OF PEPTIDE SYNTHESIS, Springer-Verlag, Berlin, 1984; E. Gross and J. Meienhofer, THE PEPTIDES, Vol. 1, 1-284 (1979); and J.M. Stewart and J.D. Young, SOLID PHASE PEPTIDE SYNTHESIS, 2d Ed., Pierce Chemical Co., Rockford, Ill., 1984. are generally illustrative of the technique and are incorporated herein by reference.

5 Synthetic methods to prepare the compounds of this invention frequently employ protective groups to mask a reactive functionality or minimize unwanted side reactions. Such protective groups are described generally in Green, T.W., PROTECTIVE GROUPS IN ORGANIC SYNTHESIS, John Wiley & Sons, New York 10 (1981). The term "amino protecting groups" generally refers to the Boc, acetyl, benzoyl, Fmoc and Cbz groups and derivatives thereof as known to the art. Methods for protection and deprotection, and replacement of an amino protecting group with another moiety are well known.

15 Acid addition salts of the compounds of formula (I) are prepared in a standard manner in a suitable solvent from the parent compound and an excess of an acid, such as hydrochloric, hydrobromic, hydrofluoric, sulfuric, phosphoric, acetic, trifluoroacetic, maleic, succinic or methanesulfonic. Certain of the compounds form inner salts or zwitterions which may be acceptable. Cationic salts are prepared by treating the parent compound with an excess of an alkaline reagent, such as a hydroxide, carbonate or 20 alkoxide, containing the appropriate cation; or with an appropriate organic amine. Cations such as Li⁺, Na⁺, K⁺, Ca⁺⁺, Mg⁺⁺ and NH₄⁺ are specific examples of cations present in pharmaceutically acceptable salts. Halides, sulfate, phosphate, alkanoates (such as acetate and trifluoroacetate), benzoates, and sulfonates (such as mesylate) are examples of anions present in pharmaceutically acceptable salts.

25 This invention also provides a pharmaceutical composition which comprises a compound according to formula (I) and a pharmaceutically acceptable carrier, diluent or excipient. Accordingly, the compounds of formula (I) may be used in the manufacture of a medicament. Pharmaceutical compositions of the compounds of formula (I) prepared as hereinbefore described may be formulated as solutions or lyophilized 30 powders for parenteral administration. Powders may be reconstituted by addition of a suitable diluent or other pharmaceutically acceptable carrier prior to use. The liquid formulation may be a buffered, isotonic, aqueous solution. Examples of suitable diluents are normal isotonic saline solution, standard 5% dextrose in water or buffered sodium or ammonium acetate solution. Such formulation is especially suitable for 35 parenteral administration, but may also be used for oral administration or contained in a metered dose inhaler or nebulizer for insufflation. It may be desirable to add excipients

such as polyvinylpyrrolidone, gelatin, hydroxy cellulose, acacia, polyethylene glycol, mannitol, sodium chloride or sodium citrate.

Alternately, these compounds may be encapsulated, tableted or prepared in an emulsion or syrup for oral administration. Pharmaceutically acceptable solid or liquid carriers may be added to enhance or stabilize the composition, or to facilitate preparation of the composition. Solid carriers include starch, lactose, calcium sulfate dihydrate, terra alba, magnesium stearate or stearic acid, talc, pectin, acacia, agar or gelatin. Liquid carriers include syrup, peanut oil, olive oil, saffine and water. The carrier may also include a sustained release material such as glyceryl monostearate or glyceryl distearate, alone or with a wax. The amount of solid carrier varies but, preferably, will be between about 20 mg to about 1 g per dosage unit. The pharmaceutical preparations are made following the conventional techniques of pharmacy involving milling, mixing, granulating, and compressing, when necessary, for tablet forms; or milling, mixing and filling for hard gelatin capsule forms. When a liquid carrier is used, the preparation will be in the form of a syrup, elixir, emulsion or an aqueous or non-aqueous suspension. Such a liquid formulation may be administered directly p.o. or filled into a soft gelatin capsule.

For rectal administration, the compounds of this invention may also be combined with excipients such as cocoa butter, glycerin, gelatin or polyethylene glycols and molded into a suppository.

The compounds of formula (I) are useful as protease inhibitors, particularly as inhibitors of cysteine and serine proteases, more particularly as inhibitors of cysteine proteases, even more particularly as inhibitors of cysteine proteases of the papain superfamily, yet more particularly as inhibitors of cysteine proteases of the cathepsin family, most particularly as inhibitors of cathepsin K. The present invention also provides useful compositions and formulations of said compounds, including pharmaceutical compositions and formulations of said compounds.

The present compounds are useful for treating diseases in which cysteine proteases are implicated, including infections by pneumocystis carinii, trypsanoma cruzi, trypsanoma brucei, and Crithidia fusciculata; as well as in schistosomiasis, malaria, tumor metastasis, metachromatic leukodystrophy, muscular dystrophy, amyotrophy; and especially diseases in which cathepsin K is implicated, most particularly diseases of excessive bone or cartilage loss, including osteoporosis, gingival disease including gingivitis and periodontitis, arthritis, more specifically, osteoarthritis and rheumatoid arthritis, Paget's disease; hypercalcemia of malignancy, and metabolic bone disease.

Metastatic neoplastic cells also typically express high levels of proteolytic enzymes that degrade the surrounding matrix, and certain tumors and metastatic neoplasias may be effectively treated with the compounds of this invention.

- The present invention also provides methods of treatment of diseases caused by pathological levels of proteases, particularly cysteine and serine proteases, more particularly cysteine proteases, even more particularly as inhibitors of cysteine proteases of the papain superfamily, yet more particularly cysteine proteases of the cathepsin family, which methods comprise administering to an animal, particularly a mammal, most particularly a human in need thereof a compound of the present invention. The present invention especially provides methods of treatment of diseases caused by pathological levels of cathepsin K, which methods comprise administering to an animal, particularly a mammal, most particularly a human in need thereof an inhibitor of cathepsin K, including a compound of the present invention. The present invention particularly provides methods for treating diseases in which cysteine proteases are implicated, including infections by pneumocystis carinii, trypsanoma cruzi, trypsanoma brucei, and Crithidia fusiculata; as well as in schistosomiasis, malaria, tumor metastasis, metachromatic leukodystrophy, muscular dystrophy, amyotrophy, and especially diseases in which cathepsin K is implicated, most particularly diseases of excessive bone or cartilage loss, including osteoporosis, gingival disease including gingivitis and periodontitis, arthritis, more specifically, osteoarthritis and rheumatoid arthritis, Paget's disease, hypercalcemia of malignancy, and metabolic bone disease.

This invention further provides a method for treating osteoporosis or inhibiting bone loss which comprises internal administration to a patient of an effective amount of a compound of formula (I), alone or in combination with other inhibitors of bone resorption, such as bisphosphonates (i.e., allendronate), hormone replacement therapy, anti-estrogens, or calcitonin. In addition, treatment with a compound of this invention and an anabolic agent, such as bone morphogenic protein, iproflavone, may be used to prevent bone loss or to increase bone mass.

For acute therapy, parenteral administration of a compound of formula (I) is preferred. An intravenous infusion of the compound in 5% dextrose in water or normal saline, or a similar formulation with suitable excipients, is most effective, although an intramuscular bolus injection is also useful. Typically, the parenteral dose will be about 0.01 to about 100 mg/kg; preferably between 0.1 and 20 mg/kg, in a manner to maintain the concentration of drug in the plasma at a concentration effective to inhibit cathepsin K. The compounds are administered one to four times daily at a level to achieve a total daily dose of about 0.4 to about 400 mg/kg/day. The precise amount of an inventive compound which is therapeutically effective, and the route by which such compound is

best administered, is readily determined by one of ordinary skill in the art by comparing the blood level of the agent to the concentration required to have a therapeutic effect.

The compounds of this invention may also be administered orally to the patient, in a manner such that the concentration of drug is sufficient to inhibit bone resorption or 5 to achieve any other therapeutic indication as disclosed herein. Typically, a pharmaceutical composition containing the compound is administered at an oral dose of between about 0.1 to about 50 mg/kg in a manner consistent with the condition of the patient. Preferably the oral dose would be about 0.5 to about 20 mg/kg.

No unacceptable toxicological effects are expected when compounds of the 10 present invention are administered in accordance with the present invention.

The compounds of this invention may be tested in one of several biological assays to determine the concentration of compound which is required to have a given pharmacological effect.

15 **Determination of cathepsin K proteolytic catalytic activity**

All assays for cathepsin K were carried out with human recombinant enzyme. Standard assay conditions for the determination of kinetic constants used a fluorogenic peptide substrate, typically Cbz-Phe-Arg-AMC, and were determined in 100 mM Na acetate at pH 5.5 containing 20 mM cysteine and 5 mM EDTA. Stock substrate 20 solutions were prepared at concentrations of 10 or 20 mM in DMSO with 20 uM final substrate concentration in the assays. All assays contained 10% DMSO. Independent experiments found that this level of DMSO had no effect on enzyme activity or kinetic constants. All assays were conducted at ambient temperature. Product fluorescence (excitation at 360 nM; emission at 460 nM) was monitored with a Perceptive 25 Biosystems Cytofluor II fluorescent plate reader. Product progress curves were generated over 20 to 30 minutes following formation of AMC product.

Inhibition studies

Potential inhibitors were evaluated using the progress curve method. Assays 30 were carried out in the presence of variable concentrations of test compound. Reactions were initiated by addition of enzyme to buffered solutions of inhibitor and substrate. Data analysis was conducted according to one of two procedures depending on the appearance of the progress curves in the presence of inhibitors. For those compounds whose progress curves were linear, apparent inhibition constants ($K_{i,app}$) were 35 calculated according to equation 1 (Brandt *et al.*, *Biochemistry*, 1989, 28, 140):

$$v = V_m A / [K_a(1 + I/K_{i,app}) + A] \quad (1)$$

where v is the velocity of the reaction with maximal velocity V_m , A is the concentration of substrate with Michaelis constant of K_m , and I is the concentration of inhibitor.

- For those compounds whose progress curves showed downward curvature
5 characteristic of time-dependent inhibition, the data from individual sets was analyzed to give k_{obs} according to equation 2:

$$[AMC] = v_{ss} t + (v_0 - v_{ss}) [I - \exp(-k_{obs}t)] / k_{obs} \quad (2)$$

- 10 where $[AMC]$ is the concentration of product formed over time t , v_0 is the initial reaction velocity and v_{ss} is the final steady state rate. Values for k_{obs} were then analyzed as a linear function of inhibitor concentration to generate an apparent second order rate constant (k_{obs} / inhibitor concentration or k_{obs} / $[I]$) describing the time-dependent inhibition. A complete discussion of this kinetic treatment has been fully
15 described (Morrison *et al.*, *Adv. Enzymol. Relat. Areas Mol. Biol.*, **1988**, *61*, 201).

- One skilled in the art would consider any compound with a K_i of less than 50 micromolar to be a potential lead compound. Preferably, the compounds used in the method of the present invention have a K_i value of less than 1 micromolar. Most preferably, said compounds have a K_i value of less than 100 nanomolar. 4-(*R,S*)-
20 Amino-N-[(8-quinolinesulfonyl)-S-leucine]-3-tetrahydrofuran-3-one, a compound of formula (I), has a K_i value that is greater than 10 micromolar.

Human Osteoclast Resorption Assay

- Aliquots of osteoclastoma-derived cell suspensions were removed from liquid
25 nitrogen storage, warmed rapidly at 37°C and washed x1 in RPMI-1640 medium by centrifugation (1000 rpm, 5 min at 4°C). The medium was aspirated and replaced with murine anti-HLA-DR antibody, diluted 1:3 in RPMI-1640 medium, and incubated for 30 min on ice. The cell suspension was mixed frequently.

- The cells were washed x2 with cold RPMI-1640 by centrifugation (1000 rpm, 5
30 min at 4°C) and then transferred to a sterile 15 mL centrifuge tube. The number of mononuclear cells were enumerated in an improved Neubauer counting chamber.

- Sufficient magnetic beads (5 / mononuclear cell), coated with goat anti-mouse IgG, were removed from their stock bottle and placed into 5 mL of fresh medium (this washes away the toxic azide preservative). The medium was removed by immobilizing
35 the beads on a magnet and is replaced with fresh medium.

- The beads were mixed with the cells and the suspension was incubated for 30 min on ice. The suspension was mixed frequently. The bead-coated cells were

immobilized on a magnet and the remaining cells (osteoclast-rich fraction) were decanted into a sterile 50 mL centrifuge tube. Fresh medium was added to the bead-coated cells to dislodge any trapped osteoclasts. This wash process was repeated x10. The bead-coated cells were discarded.

- 5 The osteoclasts were enumerated in a counting chamber, using a large-bore disposable plastic pasteur pipette to charge the chamber with the sample. The cells were pelleted by centrifugation and the density of osteoclasts adjusted to 1.5×10^4 /mL in EMEM medium, supplemented with 10% fetal calf serum and 1.7g/litre of sodium bicarbonate. 3 mL aliquots of the cell suspension (per treatment) were decanted into 10 15 mL centrifuge tubes. These cells were pelleted by centrifugation. To each tube 3 mL of the appropriate treatment was added (diluted to 50 uM in the EMEM medium). Also included were appropriate vehicle controls, a positive control (87MEM1 diluted to 100 ug/mL) and an isotype control (IgG2a diluted to 100 ug/mL). The tubes were incubate at 37°C for 30 min.
- 15 0.5 mL aliquots of the cells were seeded onto sterile dentine slices in a 48-well plate and incubated at 37°C for 2 h. Each treatment was screened in quadruplicate. The slices were washed in six changes of warm PBS (10 mL / well in a 6-well plate) and then placed into fresh treatment or control and incubated at 37°C for 48 h. The slices were then washed in phosphate buffered saline and fixed in 2% glutaraldehyde (in 0.2M sodium cacodylate) for 5 min., following which they were washed in water and incubated in buffer for 5 min at 37°C. The slices were then washed in cold water and incubated in cold acetate buffer / fast red garnet for 5 min at 4°C. Excess buffer was aspirated, and the slices were air dried following a wash in water.

- 20 The TRAP positive osteoclasts were enumerated by bright-field microscopy and 25 were then removed from the surface of the dentine by sonication. Pit volumes were determined using the Nikon/Lasertec ILM21W confocal microscope.

Examples

- Nuclear magnetic resonance spectra were recorded at either 250 or 400 MHz 30 using, respectively, a Bruker AM 250 or Bruker AC 400 spectrometer. CDCl₃ is deuteriochloroform, DMSO-d₆ is hexadeuteriodimethylsulfoxide, and CD₃OD is tetradeuteriomethanol. Chemical shifts are reported in parts per million (d) downfield from the internal standard tetramethylsilane. Abbreviations for NMR data are as follows: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, dd = doublet of doublets, dt = doublet of triplets, app = apparent, br = broad. J indicates the NMR coupling constant measured in Hertz. Continuous wave infrared (IR) spectra were recorded on a Perkin-Elmer 683 infrared spectrometer, and Fourier transform infrared

(FTIR) spectra were recorded on a Nicolet Impact 400 D infrared spectrometer. IR and FTIR spectra were recorded in transmission mode, and band positions are reported in inverse wavenumbers (cm^{-1}). Mass spectra were taken on either VG 70 FE, PE Syx API III, or VG ZAB HF instruments, using fast atom bombardment (FAB) or 5 electrospray (ES) ionization techniques. Elemental analyses were obtained using a Perkin-Elmer 240C elemental analyzer. Melting points were taken on a Thomas-Hoover melting point apparatus and are uncorrected. All temperatures are reported in degrees Centigrade ($^{\circ}\text{C}$).

Analtech Silica Gel GF and E. Merck Silica Gel 60 F-254 thin layer plates were 10 used for thin layer chromatography. Both flash and gravity chromatography were carried out on E. Merck Kieselgel 60 (230-400 mesh) silica gel.

Where indicated, certain of the materials were purchased from the Aldrich Chemical Co., Milwaukee, Wisconsin, Chemical Dynamics Corp., South Plainfield, New Jersey, and Advanced Chemtech, Louisville, Kentucky.

15 Unless otherwise indicated, all of the starting materials were obtained from commercial sources. Without further elaboration, it is believed that one skilled in the art can, using the preceding description, utilize the present invention to its fullest extent. These Examples are given to illustrate the invention, not to limit its scope. Reference is made to the claims for what is reserved to the inventors hereunder.

20

Example 1

Preparation of 3-[N^{α} -(2-quinolincarbonyl)-L-leucinyl]amino]-1-[(2S)-4-methyl-2-[[benzyloxycarbonyl]amino]pentyl]pyrrolidine

25

a.) 3-[(*tert*-butoxycarbonyl)amino]-1-[(2S)-4-methyl-2-[[benzyloxycarbonyl]amino]pentyl]pyrrolidine

To a solution of 3-(*tert*-butoxycarbonylamino)pyrrolidine (2.0 g, 10.74 mmol) in CH_2Cl_2 was added CBZ-leucinal (3.2 g, 12.88 mmol). The reaction was allowed to stir 30 at room temperature for approximately 1 hour whereupon sodium triacetoxyborohydride (3.4 g, 16.11 mmol) was added in a single portion. The reaction was stirred an additional 2 hours whereupon it was diluted with ethyl acetate and washed with sat'd NaHCO_3 , brine, dried (Na_2SO_4), concentrated and chromatographed (5% $\text{CH}_3\text{OH}:\text{CH}_2\text{Cl}_2$) to give 4.3 g of the title compound: MS(ES+) 420 (MH^+).

35

b.) 3-amino-1-[(2S)-4-methyl-2-[[[benzyloxycarbonyl]amino]pentyl]-pyrrolidine bis hydrochloride

To a solution of the compound of Example 1(a) (4.3 g) in CH₃OH (10 mL) was added 4M HCl in dioxane (10 mL). The reaction was stirred at room temperature for 4

5 hours whereupon it was concentrated *in vacuo* to yield 3.97 g of the title compound:

MS(ES+) 320 (MH⁺).

c.) 3-[[N^a-(*tert*-butoxycarbonyl)-L-leucinyl]amino]-1-[(2S)-4-methyl-2-[[[benzyloxycarbonyl]amino]pentyl]-pyrrolidine

To a solution of the compound of Example 1(b) (2.0 g, 5.1 mmole) was added

10 EDC (1.27 g, 6.37 mmol) HOBT (724 mg, 5.35 mmol) TEA (1.78 mL, 12.75 mmol) and N-BOC-leucine (1.3 g, 5.35 mmol). The reaction was stirred until complete as indicated by TLC analysis whereupon it was diluted with ethyl acetate and washed with 5% NaHCO₃, brine, dried (MgSO₄), filtered, concentrated and chromatographed (5% CH₃OH:CH₂Cl₂) to give 2.7 g of the title compound: MS(ES+) 533 (MH⁺)

15

d.) 3-L-leucinyl-1-[(2S)-4-methyl-2-[[[benzyloxycarbonyl]amino]pentyl]-pyrrolidine bis hydrochloride

Following the procedure of Example 1(b) except substituting the compound of Example 1(c), the title compound was produced: MS(ES+) 433 (MH⁺).

20

e.) 3-[[N^a-(2-quinolinecarbonyl)-L-leucinyl]amino]-1-[(2S)-4-methyl-2-[[[benzyloxycarbonyl]amino]pentyl]-pyrrolidine

Following the procedure of Example 1(c) except substituting the compound of Example 1(d) and quinaldic acid for N-BOC-leucine, the title compound was produced:

25 MS(ES+) 588 (MH⁺).

Example 2

Preparation of 1-benzyl-3-[[N^a-(2-quinolinecarbonyl)-L-leucinyl]amino]-pyrrolidine

30

a.) 1-benzyl-3-[[N^a-(*tert*-butoxycarbonyl)-L-leucinyl]amino]-pyrrolidine

Following the procedure of Example 1(c) except substituting 1-benzyl-3-aminopyrrolidine, the title compound was prepared. MS(ES+) 390 (MH⁺).

35

b.) 1-benzyl-3-L-leucinyl-pyrrolidine bis hydrochloride

Following the procedure of Example 1(b) except substituting the compound of Example 2(a), the title compound was prepared: MS(ES+) 290 (MH⁺).

c.) 1-benzyl-3-[[N^a-(2-quinolinecarbonyl)-L-leucinyl]amino]-pyrrolidine

Following the procedure of Example 1(e) except substituting the compound of Example 2(b), the title compound was prepared: MS(ES+) 445 (MH⁺).

5

Example 3Preparation of 3-[[N^a-(2-naphthylcarbonyl)-L-leucinyl]amino]-1-[(2S)-4-methyl-2-[(benzyloxycarbonyl)amino]pentyl]-pyrrolidine

10

Following the procedure of Example 1(e) except substituting 2-naphthoic acid for quinaldic acid, the title compound was prepared: MS(ES+) 587 (MH⁺).

Example 4

15

Preparation of 1-benzyl-3-[[N^a-(2-naphthylcarbonyl)-L-leucinyl]amino]-pyrrolidine

Following the procedure of Example 2(c) except substituting 2-naphthoic acid for quinaldic acid, the title compound was produced: MS(ES+) 444 (MH⁺).

20

Example 5Preparation of 1-benzyl-((3S))-[[N^a-(benzyloxycarbonyl)-L-leucinyl]aminol-pyrrolidinea.) 1-benzyl-((3S))-(*tert*-butoxycarbonyl)amino-pyrrolidine

Following the procedure of Example 1(a) except substituting ((3S))-(-)-3-(*tert*-butoxycarbonylamino)pyrrolidine for 3-(*tert*-butoxycarbonylamino)pyrrolidine and benzaldehyde for CBZ-leucinal, the title compound was prepared: MS(ES+) 221.2 (M-C₄H₈), 277.3 (MH⁺).

b.) 1-benzyl-((3S))-amino-pyrrolidine bis hydrochloride

30

To a solution of the compound of Example 5(a) in methanol was added a 1M HCl/ether. The reaction was stirred at room temperature until complete as indicated by mass spectral analysis. The reaction was concentrated *in vacuo* to give a white solid: MS(ES+) 177.0 (MH⁺).

c.) 1-benzyl-((3S))-[[N^a-(benzyloxycarbonyl)-L-leucinyl]amino]-pyrrolidine

Following the procedure of Example 1(c) except substituting the compound of Example 5(b) and CBZ-leucine for BOC-leucine, the title compound was prepared: MS(ES+) 424.2(MH⁺).

5

Example 6Preparation of 1-benzyl-((3S))-[[N^a-(tert-butoxycarbonyl)-L-leucinyl]amino]-pyrrolidine

10 Following the procedure of Example 5(c) except substituting BOC-leucine for CBZ-leucine, the title compound was prepared: MS(ES+) 390.5 (MH⁺).

Example 715 Preparation of ((3S))-[[N^a-(2-naphthylcarbonyl)-L-leucinyl]amino]-1-[(2S)-4-methyl-2-[[benzyloxycarbonyl]amino]pentyl]-pyrrolidine

a.) ((3S))-[(tert-butoxycarbonyl)amino]-1-[(2S)-4-methyl-2-[[benzyloxycarbonyl]amino]pentyl]-pyrrolidine

20 Following the procedure of Example 1(a) except substituting ((3S))-(-)-3-(tert-butoxycarbonylamino)pyrrolidine for 3-(tert-butoxycarbonylamino)pyrrolidine the title compound was prepared: MS(ES+) 420 (MH⁺).

b.) ((3S))-[(tert-butoxycarbonyl)amino]-1-[(2S)-4-methyl-2-[[benzyloxycarbonyl]amino]pentyl]-pyrrolidine

25 Following the procedure of Example 1(b) except substituting the compound of Example 7(a), the title compound was produced: MS(ES) 320 (MH⁺)

c.) (3S)-[[N^a-(tert-butoxycarbonyl)-L-leucinyl]amino]-1-[(2S)-4-methyl-2-

30 [[benzyloxycarbonyl]amino]pentyl]-pyrrolidine

Following the procedure of Example 1(c) except substituting the compound of Example 7(b), the title compound was produced: MS(ES+) 533 (MH⁺).

d.) (3S)-L-leucinyl-1-[(2S)-4-methyl-2-[[benzyloxycarbonyl]amino]pentyl]-pyrrolidine

35 bis hydrochloride

Following the procedure of Example 1(d) except substituting the compound of Example 7(c), the title compound was prepared: MS(ES+) 433 (MH⁺).

e.) (3S)-[[N^a-(2-naphthylcarbonyl)-L-leucinyl]amino]-1-[(2S)-4-methyl-2-[(benzyloxycarbonyl)amino]pentyl]-pyrrolidine

Following the procedure of Example 1(e) except substituting the compound of
5 Example 7(d) and substituting 2-naphthoic acid for quinaldic acid, the title compound
was produced: MS(ES+) 587 (MH⁺).

Example 8

10 Preparation of (3R)-[[N^a-(2-naphthylcarbonyl)-L-leucinyl]amino]-1-[(2S)-4-methyl-2-[(benzyloxycarbonyl)amino]pentyl]-pyrrolidine

a.) (3R)-[(*tert*-butoxycarbonyl)amino]-1-[(2S)-4-methyl-2-[(benzyloxycarbonyl)amino]pentyl]-pyrrolidine

15 Following the procedure of Example 1(a) except substituting (3R)-(-)-3-(*tert*-butoxycarbonylamino)pyrrolidine for 3-(*tert*-butoxycarbonylamino)pyrrolidine the title compound was prepared: MS(ES+) 420 (MH⁺).

b.) (3R)-amino-1-[(2S)-4-methyl-2-[(benzyloxycarbonyl)amino]pentyl]-pyrrolidine

20 Following the procedure of Example 1(b) except substituting the compound of Example 8(a), the title compound was produced: 320 MS(ES) (MH⁺)

c.) (3R)-[[N^a-(*tert*-butoxycarbonyl)-L-leucinyl]amino]-1-[(2S)-4-methyl-2-[(benzyloxycarbonyl)amino]pentyl]-pyrrolidine

25 Following the procedure of Example 1(c) except substituting the compound of Example 8(b), the title compound was produced: 533 MS(ES+) (MH⁺).

d.) (3R)-L-leucinyl-1-[(2S)-4-methyl-2-[(benzyloxycarbonyl)amino]pentyl]-pyrrolidine bis hydrochloride

30 Following the procedure of Example 1(d) except substituting the compound of Example 8(c), the title compound was prepared: MS(ES+) 433 (MH⁺).

e.) (3R)-[[N^a-(2-naphthylcarbonyl)-L-leucinyl]amino]-1-[(2S)-4-methyl-2-[(benzyloxycarbonyl)amino]pentyl]-pyrrolidine

35 Following the procedure of Example 1(e) except substituting the compound of Example 8(d) and substituting 2-naphthoic acid for quinaldic acid, the title compound was produced: MS(ES+) 587 (MH⁺).

Example 9Preparation of 1-benzyl-(3R)-[[N^a-(2-quinolineacetonoyl)-L-leucinyl]amino]-pyrrolidine

5

a.) 1-benzyl-(3R)-[(*tert*-butoxycarbonyl)amino]-pyrrolidine

To a solution of ((3R))-(-)-3-(*tert*-butoxycarbonylamino)pyrrolidine (2.0 g, 10.73 mmol) in CH₂Cl₂ (20 mL) was added benzaldehyde (1.3 mL, 12.88 mmol). The reaction was stirred at room temperature for 2 hours whereupon sodium triacetoxyborohydride (5.68 g, 26.82 mmol) was added. The reaction was stirred overnight at room temperature whereupon it was diluted with ethyl acetate and washed with sat. K₂CO₃, water, brine, dried (MgSO₄), filtered, concentrated and chromatographed (1:1 hex:EtOAc) to give the title compound: MS(ES+) 221.1 (M-C₄H₈), 277.2 (MH⁺)

15

b.) 1-benzyl-(3R)-amino-pyrrolidine bis hydrochloride

To a solution of the compound of Example 9(a) in methanol was added 1N HCl/ether. The suspension was stirred at room temperature until complete as indicated by mass spectral analysis. The reaction was concentrated *in vacuo* to give the title compound: MS(ES+) 176.9 (MH⁺).

20

c.) 1-benzyl-(3R)-[[N^a-(*tert*-butoxycarbonyl)-L-leucinyl]amino]-pyrrolidine

Following the procedure of Example 1(c) except substituting the compound of Example 9(b) and N-methylmorpholine for triethylamine, the title compound was produced: MS(ES+) 390.3 (MH⁺).

25

d.) 1-benzyl-(3R)-[(L-leucinyl)amino]-pyrrolidine bis hydrochloride

To a solution of the compound of Example 9(c) in ethyl acetate and methanol was bubbled HCl gas for ca. 2 mins. The reaction was stirred overnight whereupon it was concentrated in vacuo to afford the title compound: MS(ES+) 290.4 (MH⁺).

30

e.) 1-benzyl-(3R)-[[N^a-(2-naphthylacetonoyl)-L-leucinyl]amino]-pyrrolidine

To a suspension of the compound of Example 9(d) (75 mg) was added EDC (44.3 mg), HOBT (28.4 mg) NMM (0.14 mL) and 2-naphthylacetic acid. The reaction was stirred overnight at room temperature whereupon it was diluted with ethyl acetate and washed with sat. K₂CO₃, water, brine, dried (MgSO₄), filtered, concentrated and chromatographed to give the title compound: MS(ES+) 458.3 (MH⁺).

Example 10Preparation of 1-benzyl-(3R)-[[N^a-(2-naphthylcarbonyl)-L-leucinyl]amino]-pyrrolidine

5

Following the procedure of Example 9(e) except substituting 2-naphthoic acid for 2-naphthylacetic acid, the title compound was prepared: MS(ES+) 444.2 (MH⁺).

Example 11

10

Preparation of 1-benzyl-(3R)-[[N^a-(3-quinolinecarbonyl)-L-leucinyl]amino]-pyrrolidine

Following the procedure of Example 9(e) except substituting 3-quinolinecarboxylic acid for 2-naphthylacetic acid, the title compound was prepared:
15 MS(ES+) 445.3 (MH⁺).

Example 12Preparation of 1-benzyl-(3R)-[[N^a-(2-quinolinecarbonyl)-L-leucinyl]amino]-pyrrolidine

20

Following the procedure of Example 9(e) except substituting quinaldic acid for 2-naphthylacetic acid, the title compound was prepared: MS(ES+) 445.2 (MH⁺).

Example 13

25

Preparation of 1-benzyl-(3R)-[[N^a-(3-isoquinolinecarbonyl)-L-leucinyl]amino]-pyrrolidine

Following the procedure of Example 9(e) except substituting 3-isoquinolinecarboxylic acid for 2-naphthylacetic acid, the title compound was prepared:
30 MS(ES+) 445.3 (MH⁺).

Example 14Preparation of 1-benzyl-(3S)-[[N^a-(2-naphthylacetonoyl)-L-leucinyl]amino]-pyrrolidine

- 5 a.) 1-benzyl-(3S)-[(*tert*-butoxycarbonyl)amino]-pyrrolidine

Following the procedure of Example 9(a) except substituting ((3S))-(-)-3-(*tert*-butoxycarbonylamino)pyrrolidine for (3R)-(-)-3-(*tert*-butoxycarbonylamino)pyrrolidine, the title compound was produced: MS(ES+) 277.2 (MH⁺).

- 10 b.) 1-benzyl-(3S)-amino-pyrrolidine bis hydrochloride

Following the procedure of Example 9(b) except substituting the compound of example 14(a), the title compound was produced: MS(ES+) 177.0 (MH⁺).

- c.) 1-benzyl-(3S)-[[N^a-(*tert*-butoxycarbonyl)-L-leucinyl]amino]-pyrrolidine

15 Following the procedure of Example 9(c) except substituting the compound of Example 14(b), the title compound was produced: MS(ES+) 390.3 (MH⁺).

- d.) 1-benzyl-(3S)-[(L-leucinyl)amino]-pyrrolidine bis hydrochloride

20 Following the procedure of Example 9(d) except substituting the compound of Example 14(c), the title compound was produced: MS(ES+) 290.3 (MH⁺).

- e.) 1-benzyl-(3S)-[[N^a-(2-naphthylacetonoyl)-L-leucinyl]amino]-pyrrolidine

Following the procedure of Example 9(e) except substituting the compound of Example 14(d), the title compound was produced: MS(ES+) 458.4 (MH⁺).

25

Example 15Preparation of 1-benzyl-(3S)-[[N^a-(2-naphthylcarbonyl)-L-leucinyl]amino]-pyrrolidine

30 Following the procedure of Example 14(e) except substituting 2-naphthoic acid for 2-naphthylacetic acid, the title compound was produced: MS(ES+) 444.4 (MH⁺).

Example 16Preparation of 1-benzyl-(3S)-[[N^a-(3-quinolinecarbonyl)-L-leucinyl]amino]-pyrrolidine

5 Following the procedure of Example 14(e) except substituting 3-quinolinecarboxylic acid for 2-naphthylacetic acid, the title compound was produced: MS(ES+) 445.2 (MH⁺).

Example 17

10

Preparation of 1-benzyl-(3S)-[[N^a-(2-quinolinecarbonyl)-L-leucinyl]amino]-pyrrolidine

Following the procedure of Example 14(e) except substituting quinaldic acid for 2-naphthylacetic acid, the title compound was produced: MS(ES+) 445.3 (MH⁺).

15

Example 18Preparation of 1-benzyl-(3S)-[[N^a-(3-isoquinolinecarbonyl)-L-leucinyl]amino]-pyrrolidine

20

Following the procedure of Example 14(e) except substituting 3-isoquinolinecarboxylic acid for 2-naphthylacetic acid, the title compound was produced: MS(ES+) 445.3 (MH⁺).

25

Example 19Preparation of 1-benzyl-4-[[N^a-(2-naphthylcarbonyl)-L-leucinyl]amino]-piperidinea.) 1-benzyl-4-[[N^a-(*tert*-butoxycarbonyl)-L-leucinyl]amino]-piperidine

30 Following the procedure of Example 1(c) except substituting 4-amino-1-benzylpiperidine, the title compound was produced: MS(ES+) 404.1 (MH⁺).

b.) 1-benzyl-4-[(L-leucinyl)amino]-piperidine

The compound of Example 19(a) (2.0 g) was dissolved in 4N HCl/dioxane (100 mL). The reaction was stirred at room temperature for 30 minutes whereupon it was concentrated in vacuo to give 1.94 g of the title compound as a white solid: MS(ES+) 304.2 (MH⁺).

c.) 1-benzyl-4-[[N^a-(2-naphthylcarbonyl)-L-leucinyl]amino]-piperidine

To a solution of the compound of Example 19(b) (240 mg) in DMF (3.0 mL) was added N-methylmorpholine (0.17 mL), HOBT (101.5 mg), 2-naphthoic acid (130.2 mg) and EDC (145.4 mg). The reaction was stirred overnight whereupon it was poured into a rapidly stirred mixture of EtOAc, 10% Na₂CO₃ and brine (75 mL each). This mixture was stirred for 30 minutes. The organic layer was separated and the aqueous layer was washed with ethyl acetate. The combined organic layers were washed with 10% Na₂CO₃, water, brine, dried (MgSO₄), filtered, concentrated and chromatographed (ethyl acetate) to give 107 mg of the title compound: MS(ES+) 458.5 (MH⁺).

Example 20

Preparation of 1-benzyl-4-[[N^a-(2-quinolinecarbonyl)-L-leucinyl]amino]-piperidine

Following the procedure of Example 19(c) except substituting quinaldic acid for 2-naphthoic acid, the title compound was prepared: MS(ES+) 459.3 (MH⁺).

Example 21

Preparation of 1-benzyl-4-[[N^a-(benzyloxycarbonyl)-L-leucinyl]amino]-piperidine

To a solution of N-benzyl-4-amino piperidine (0.50 g) in CH₂Cl₂ (10 mL) was added CBZ-leucine (695 mg), EDC (552.5 mg) and HOBT (356.6 mg). The reaction was stirred at room temperature until complete as indicated by TLC analysis. The reaction was dissolved in CHCl₃ and washed with 10% Na₂CO₃, brine, dried (MgSO₄), filtered, concentrated and chromatographed (3:1 EtOAc:hexanes) to give 0.99 g of the title compound: MS(ES+) 438 (MH⁺).

Example 22

Preparation of 1-[3-(2-pyridyl)phenyl]-2-ethyl-(3S)-[[N^a-(2-naphthylcarbonyl)-L-leucinyl]amino]-pyrrolidine

35 a) N-methyl-N-methoxy-3-(2-pyridyl)-phenylacetamide

To a stirred solution of N-methoxy-N-methylamine hydrochloride (0.980 g, 10.0 mmol) in DMF (25 mL) was added N-methylmorpholine (1.21 mL, 11.0 mmol), HOBr (1.50 g, 11.1

mmol), 3-(2-pyridyl)-phenylacetic acid (2.36 g, 11.1 mmol), and EDC (2.13 g, 11.1 mmol). The reaction was stirred overnight whereupon it was poured into a rapidly-stirred mixture of 150 mL each of EtOAc, 10% NaHCO₃, and brine. After stirring for 30 min, the layers were separated and the aqueous layer was washed with fresh EtOAc (150 mL). The combined organic layers 5 were washed with 10% Na₂CO₃, and brine, then dried (MgSO₄), filtered, and concentrated. Column chromatography (silica gel, 3:1 EtOAc: hexane) gave 2.275 g of the title compound: MS (ES+) (MH⁺) 257.2.

b) 3-(2-pyridyl)-phenylacetaldehyde

10 To a stirred solution of the compound of Example 22(a) (2.2 g, 8.6 mmol) in anhydrous THF (20 mL) at -78°C was added a solution of lithium aluminum hydride in THF (22 mL, 22.0 mmol). The reaction was stirred for 2 h, then warmed to 0°C and stirred 1 h, whereupon 4.2 g of KHSO₄ was added in small portions over 10 min, followed by 100 mL of water in small portions. The reaction mixture was filtered to remove a white precipitate and the filtrate was 15 adjusted to pH 9 by the addition of 1 N NaOH, then extracted with Et₂O (3 x 100 mL). The combined organic layers were washed with brine, then dried (Na₂SO₄), filtered, and concentrated to give 1.878 g of the title compound: MS (ES+) (MH⁺) 198.1.

c) 1-[3-(2-pyridyl)phenyl]-2-ethyl-(3S)-[N^α-(*tert*-butoxycarbonylamino)-pyrrolidine

20 To a stirred solution of (3S)-(--)3-(*tert*-butoxycarbonylamino)pyrrolidine (672.3 mg, 3.6 mmol) in CH₂Cl₂ (15 mL) was added the compound of Example 22(b) (0.94 g, 4.3 mmol). The reaction was stirred 2 h whereupon Na(OAc)₂BH (1.68 g, 7.9 mmol) added. After stirring overnight, the reaction mixture was diluted with CHCl₃ (150 mL) and washed with H₂O, and brine, then dried (MgSO₄), filtered, and concentrated. Column chromatography (silica gel, 1:9 25 MeOH: EtOAc) gave 467 mg of the title compound: MS (ES+) (MH⁺) 368.

d) 1-[3-(2-pyridyl)phenyl]-2-ethyl-(3S)-[[N^α-(*tert*-butoxycarbonyl)-L-leucinyl]amino]-pyrrolidine

30 The compound of Example 22(c) (440 mg, 1.2 mmol) was dissolved in 4.0 N HCl in dioxane (20 mL) and stirred at room temperature for 30 min. The solution was concentrated to a white solid and dried under high vacuum for 30 min. To a stirred solution of the residue in DMF (10 mL) was added N-methylmorpholine (400 uL, 3.6 mmol), HOEt (245.6 mg, 1.8 mmol), Boc-Leucine hydrate (449.1 mg, 1.8 mmol), and EDC (352.0 mg, 1.8 mmol). The reaction was stirred overnight whereupon it was partitioned between 50 mL each of EtOAc, 10% 35 Na₂CO₃, and brine. The aqueous layer was washed with fresh EtOAc (50 mL), the combined organic layers were washed with 10% Na₂CO₃ and brine, then dried (MgSO₄), filtered, and

concentrated. Column chromatography (silica gel, 5:95 MeOH: EtOAc) gave 204 mg of the title compound: MS (ES+) (MH+) 481.4.

e) 1-[3-(2-pyridyl)phenyl]-2-ethyl-(3S)-[[N^α-L-leucinyl]amino]-pyrrolidine dihydrochloride

5 The compound of Example 22(d) (200 mg, 0.42 mmol) was dissolved in 4.0 N HCl in dioxane (25 mL) and stirred at room temperature for 1 h. The solution was concentrated to a white solid and dried under high vacuum for 3 h to give the title compound: MS (ES+) (MH+) 381.4.

10 f) 1-[3-(2-pyridyl)phenyl]-2-ethyl-(3S)-[[N^α-(2-naphthylcarbonyl)-L-leucinyl]amino]-pyrrolidine

To a stirred solution of the compound of Example 22(e) (0.14 mmol) in DMF (2 mL) was added N-methylmorpholine (62 uL, 0.56 mmol), HOBr (31.8 mg, 0.24 mmol), 2-naphthoic acid (37.6 mg, 0.22 mmol), and EDC (41.2 mg, 0.22 mmol). The reaction was stirred overnight 15 whereupon it was partitioned between 50 mL each of EtOAc, 10% Na₂CO₃, and brine. The aqueous layer was washed with fresh EtOAc (50 mL), the combined organic layers were washed with 10% Na₂CO₃ and brine, then dried (MgSO₄), filtered, and concentrated. Column chromatography (silica gel, 5:95 MeOH: EtOAc) gave 40.1 mg of the title compound: MS (ES+) (MH+) 535.4.

20

Example 23

Preparation of 1-[3-(2-pyridyl)phenyl]-2-ethyl-(3S)-[[N^α-(2-quinolinecarbonyl)-L-leucinyl]amino]-pyrrolidine

25

Following the procedure of Example 22(f), except using 2-quinolinecarboxylic acid, the title compound was prepared: MS (ES+) (MH+) 536.4.

Example 24

30

Preparation of 1-[3-(2-pyridyl)phenyl]-2-ethyl-(3S)-[[N^α-(3-isoquinolinecarbonyl)-L-leucinyl]amino]-pyrrolidine

35

Following the procedure of Example 22(f), except using 3-isoquinolinecarboxylic acid, the title compound was prepared: MS (ES+) (MH+) 536.4.

Example 25Preparation of 1-[3-(2-pyridyl)phenyl]-2-ethyl-(3R)-[[N^α-(2-naphthylcarbonyl)-L-leucinyl]amino]-pyrrolidine

5

- a) 1-[3-(2-pyridyl)phenyl]-2-ethyl-(3R)-[N^α-(*tert*-butoxycarbonylamino)-pyrrolidine

Following the procedure of Example 22(c), except substituting (3R)-(+) -3-(*tert*-butoxycarbonylamino)pyrrolidine, the title compound was prepared: MS (ES+) (MH⁺) 368.4.

- 10 b) 1-[3-(2-pyridyl)phenyl]-2-ethyl-(3R)-[[N^α-(*tert*-butoxycarbonyl)-L-leucinyl]amino]-pyrrolidine

Following the procedure of Example 22 (d), except substituting the compound of Example 25 (a), the title compound was prepared: MS (ES+) (MH⁺) 481.4.

- 15 c) 1-[3-(2-pyridyl)phenyl]-2-ethyl-(3R)-[[N^α-L-leucinyl]amino]-pyrrolidine dihydrochloride

Following the procedure of Example 22 (e), except substituting the compound of Example 25 (b), the title compound was prepared: MS (ES+) (MH⁺) 381.4.

- 20 d) 1-[3-(2-pyridyl)phenyl]-2-ethyl-(3R)-[[N^α-(2-naphthylcarbonyl)-L-leucinyl]amino]-pyrrolidine

Following the procedure of Example 22 (f), except substituting the compound of Example 25 (c), the title compound was prepared: MS (ES+) (MH⁺) 535.3.

Example 26

25

Preparation of 1-[3-(2-pyridyl)phenyl]-2-ethyl-(3R)-[[N^α-(3-isoquinolinecarbonyl)-L-leucinyl]amino]-pyrrolidine

- 30 Following the procedure of Example 25(d), except using 3-isoquinolinecarboxylic acid, the title compound was prepared: MS (ES+) (MH⁺) 536.3.

Example 27Preparation of 1-[3-(2-pyridyl)phenyl]-2-ethyl-(3R)-[[N^α-(2-quinolinecarbonyl)-L-leucinyl]amino]-pyrrolidine

5

Following the procedure of Example 25(d), except using 2-quinolinecarboxylic acid, the title compound was prepared: MS (ES+) (MH+) 536.3.

Example 28

10

Preparation of 1-(1-adamantanecarbonyl)-(3R)-[[N^α-(4-pyridylmethoxycarbonyl)-L-leucinyl]amino]-pyrrolidine

a) 1-(1-adamantanecarbonyl)-(3R)-[[N^α-(*tert*-butyloxycarbonyl)-L-leucinyl]amino]-pyrrolidine
15 To a stirred solution of (3R)-(+)-3-(*tert*-butoxycarbonylamino)pyrrolidine (1.87 g, 10.0 mmol) in CH₂Cl₂ (30 mL) at 0°C was added N-methylmorpholine (1.65 mL, 15.0 mmol) and 1-adamantylcarbonyl chloride (2.99 g, 15.0 mmol). The reaction was stirred overnight, gradually warming to room temperature, whereupon it was diluted with 200 mL of CHCl₃, washed with 5% NaHCO₃, H₂O, 1N HCl, H₂O, and brine, then dried (MgSO₄), filtered, and concentrated to 20 give 4.66 g of the title compound: MS (ES+) (MH+) 349.4.

b) 1-(1-adamantanecarbonyl)-(3R)-aminopyrrolidine hydrochloride

The compound of Example 28 (a) (4.6 g) was dissolved in 4.0 N HCl in dioxane (100 mL) and stirred at room temperature for 1 h. The solution was concentrated to a white solid and 25 dried under high vacuum for 2 h to give the title compound: MS (ES+) (MH+) 249.1.

c) 1-(1-adamantanecarbonyl)-(3R)-[[N^α-(4-pyridylmethoxycarbonyl)-L-leucinyl]amino]-pyrrolidine

To a stirred solution of the compound of Example 28(b) (143.2 mg, 0.50 mmol) in DMF 30 (2 mL) was added N-methylmorpholine (83 uL, 0.75 mmol), HOBr (101.5 mg, 0.75 mmol), 4-Inoc-Leucine (201.5 mg, 0.76 mmol), and EDC (146.0 mg, 0.76 mmol). The reaction was stirred overnight whereupon it was partitioned between 50 mL each of EtOAc, 10% Na₂CO₃, and brine. The aqueous layer was washed with fresh EtOAc (50 mL), the combined organic layers were washed with 10% Na₂CO₃ and brine, then dried (MgSO₄), filtered, and 35 concentrated. Column chromatography (silica gel, 2:98 MeOH: EtOAc) gave 109.0 mg of the title compound: MS (ES+) (MH+) 497.5.

Example 29Preparation of 1-(1-adamantanecarbonyl)-(3S)-[[N^α-(4-pyridylmethoxycarbonyl)-L-leucinyl]amino]pyrrolidine

5

- a) 1-(1-adamantanecarbonyl)-(3S)-[[N^α-(*tert*-butyloxycarbonyl)-L-leucinyl]amino]pyrrolidine

Following the procedure of Example 28(a), except substituting (3S)-(−)-3-(*tert*-butoxycarbonylamino)pyrrolidine, the title compound was prepared: MS (ES+) (MH⁺) 349.5.

10

- b) 1-(1-adamantanecarbonyl)-(3S)-aminopyrrolidine hydrochloride

Following the procedure of Example 28(b), except substituting the compound of Example 29 (a), the title compound was prepared: MS (ES+) (MH⁺) 249.1.

15

- c) 1-(1-adamantanecarbonyl)-(3S)-[[N^α-(4-pyridylmethoxycarbonyl)-L-leucinyl]amino]pyrrolidine

Following the procedure of Example 28(c), except substituting the compound of Example 29(b), the title compound was prepared: MS (ES+) (MH⁺) 497.4.

Example 30

20

Preparation of (3R)-[[N^α-(benzo[b]thiophene-2-carbonyl)-L-leucinyl]amino]-1-[(2S)-4-methyl-2-[(benzyloxycarbonyl)amino]pentyl]pyrrolidine

25

- a) (3R)-[[N^α-(*tert*-butoxycarbonyl)amino]-1-[(2S)-4-methyl-2-

[(benzyloxycarbonyl)amino]pentyl]pyrrolidine

To a stirred solution of (3R)-(+)3-(*tert*-butoxycarbonylamino)pyrrolidine (2 g, 10.7 mmol) in CH₂Cl₂ (200 mL) was added N-CBZ-Leucinal (3.2 g, 12.9 mmol). The reaction was stirred 2 h whereupon Na(OAc)₂BH (3.4 g, 16.1 mmol) was added. After stirring overnight, the reaction mixture was diluted with CHCl₃ (150 mL) and washed with 5% NaHCO₃ and brine, then dried (MgSO₄), filtered, and concentrated. Column chromatography (silica gel, 3:97 MeOH: CH₂Cl₂) gave 3.4 g of the title compound: MS (ES+) (MH⁺) 420.

30

- b) (3R)-amino-1-[(2S)-4-methyl-2-[(benzyloxycarbonyl)amino]pentyl]pyrrolidine dihydrochloride

35

The compound of Example 30 (a) (3.4 g) was dissolved in 4.0 N HCl in dioxane (50 mL) and stirred at room temperature for 1 h. The solution was concentrated *in vacuo* and dried under high vacuum to give 3.37 g of the title compound: MS (ES+) (MH⁺) 320.

c) (3R)-[[N^α-(*tert*-butoxycarbonyl)-L-leucinyl]amino]-1-[(2S)-4-methyl-2-[(benzyloxycarbonyl)amino]pentyl]-pyrrolidine

To a stirred solution of the compound of Example 30(b) (2.36 g, 6.0 mmol) in DMF (25 mL) was added N-methylmorpholine (2.0 mL, 18.2 mmol), HOBr (1.22 g, 9.0 mmol), Boc-Leucine hydrate (2.25 g, 9.0 mmol), and EDC (1.73 g, 9.0 mmol). The reaction was stirred for 3 h whereupon it was partitioned between 150 mL each of EtOAc, 10% Na₂CO₃, and brine. The aqueous layer was washed with fresh EtOAc (150 mL), the combined organic layers were washed with 10% Na₂CO₃ and brine, then dried (MgSO₄), filtered, and concentrated. Column chromatography (silica gel, 2:1 EtOAc: hexane) gave 2.78 g of the title compound: MS (ES+) (MH⁺) 533.6.

d) (3R)-[[N^α-L-leucinyl]amino]-1-[(2S)-4-methyl-2-[(benzyloxycarbonyl)amino]pentyl]-pyrrolidine dihydrochloride

The compound of Example 30(c) (2.7 g) was dissolved in 4.0 N HCl in dioxane (100 mL) and stirred at room temperature for 1 h. The solution was concentrated in vacuo and dried azeotropically with toluene to afford a tan solid and stored under high vacuum overnight to give 2.45 g of the title compound: MS (ES+) (MH⁺) 433.3.

e) (3R)-[[N^α-(benzo[b]thiophene-2-carbonyl)-L-leucinyl]amino]-1-[(2S)-4-methyl-2-[(benzyloxycarbonyl)amino]pentyl]-pyrrolidine

To a stirred solution of the compound of Example 30(d) (101.4 mg, 0.2 mmol) in DMF (1 mL) was added N-methylmorpholine (66 uL, 0.6 mmol), HOBr (42.2 mg, 0.3 mmol), benzo[b]thiophene-2-carboxylic acid (53.3 mg, 0.3 mmol), and EDC (57.8 mg, 0.3 mmol). The reaction was stirred overnight whereupon it was partitioned between 50 mL each of EtOAc, 10% Na₂CO₃, and brine. The aqueous layer was washed with fresh EtOAc (50 mL), the combined organic layers were washed with 10% Na₂CO₃ and brine, then dried (MgSO₄), filtered, and concentrated. Column chromatography (silica gel, 3:1 EtOAc: hexane) gave 80.4 mg of the title compound: MS (ES+) (MH⁺) 593.4.

30

Example 31

Preparation of (3R)-[[N^α-(3,4-dimethoxybenzoyl)-L-leucinyl]amino]-1-[(2S)-4-methyl-2-[(benzyloxycarbonyl)amino]pentyl]-pyrrolidine

35

Following the procedure of Example 30(e), except substituting 3,4-dimethoxybenzoic acid, the title compound was prepared: MS (ES+) (MH⁺) 597.4.

Example 32

- 5 Preparation of (3R)-[N^α-(benzofuran-2-carbonyl)-L-leucinyl]amino]-1-[(2S)-4-methyl-2-[[(benzyloxycarbonyl)amino]pentyl]-pyrrolidine

Following the procedure of Example 30(e), except substituting benzofuran-2-carboxylic acid, the title compound was prepared: MS (ES+) (MH+) 577.2.

10

Example 33

- Preparation of (3R)-[N^α-(benzothiazole-6-carbonyl)-L-leucinyl]amino]-1-[(2S)-4-methyl-2-[[(benzyloxycarbonyl)amino]pentyl]-pyrrolidine

15

Following the procedure of Example 30(e), except substituting benzothiazole-6-carboxylic acid, the title compound was prepared: MS (ES+) (MH+) 594.4.

Example 34

- 20 Preparation of (3R)-[N^α-(indole-2-carbonyl)-L-leucinyl]amino]-1-[(2S)-4-methyl-2-[[(benzyloxycarbonyl)amino]pentyl]-pyrrolidine

25

Following the procedure of Example 30(e), except substituting indole-2-carboxylic acid, the title compound was prepared: MS (ES+) (MH+) 576.3.

Example 35

30

- Preparation of (3R)-[N^α-(4-fluorobenzoyl)-L-leucinyl]amino]-1-[(2S)-4-methyl-2-[[(benzyloxycarbonyl)amino]pentyl]-pyrrolidine

Following the procedure of Example 30(e), except substituting 4-fluorobenzoic acid, the title compound was prepared: MS (ES+) (MH+) 555.3.

Example 36Preparation of (3R)-[[N^α-(4-methoxybenzoyl)-L-leucinyl]amino]-1-[(2S)-4-methyl-2-[(benzyloxycarbonyl)amino]pentyl]-pyrrolidine

5

Following the procedure of Example 30(e), except substituting p-4-methoxybenzoic acid, the title compound was prepared: MS (ES+) (MH+) 567.4.

Example 37

10

Preparation of (3R)-[[N^α-(3,4-dichlorobenzoyl)-L-leucinyl]amino]-1-[(2S)-4-methyl-2-[(benzyloxycarbonyl)amino]pentyl]-pyrrolidine

15

Following the procedure of Example 1(e), except substituting 3,4-dichlorobenzoic acid, the title compound was prepared: MS (ES+) (MH+) 605.2.

Example 38

20

Preparation of (3R)-[[N^α-(thiophene-2-carbonyl)-L-leucinyl]amino]-1-[(2S)-4-methyl-2-[(benzyloxycarbonyl)amino]pentyl]-pyrrolidine

Following the procedure of Example 30(e), except substituting thiophene-3-carboxylic acid, the title compound was prepared: MS (ES+) (MH+) 543.4.

25

Example 39Preparation of (3R)-[[N^α-(4-biphenylcarbonyl)-L-leucinyl]amino]-1-[(2S)-4-methyl-2-[(benzyloxycarbonyl)amino]pentyl]-pyrrolidine

30

To a stirred solution of the compound of Example 30(d) (102.3 mg, 0.2 mmol) in CH₂Cl₂ (1 mL) at 0°C was added N-methylmorpholine (66 uL, 0.6 mmol) and 4-biphenylcarbonyl chloride (65.2 mg, 0.3 mmol). The reaction was stirred overnight whereupon it was diluted with CHCl₃ and washed with 10% Na₂CO₃ and brine, then dried (MgSO₄), filtered, and concentrated. Column chromatography (silica gel, 3:1 EtOAc: hexane) gave 55.1 mg of the title compound: MS (ES+) (MH+) 613.5.

Example 40

Preparation of (3R)-[[N^α-(5-methoxybenzofuran-2-carbonyl)-L-leucinyl]amino]-1-[(2S)-4-methyl-2-[(benzyloxycarbonyl)amino]pentyl]-pyrrolidine

5

Following the procedure of Example 30(e), except substituting 5-methoxybenzofuran-2-carboxylic acid, the title compound was prepared: MS (ES+) (MH+) 607.4.

Example 41

10

Preparation of (3R)-[[N^α-(5-chlorobenzofuran-2-carbonyl)-L-leucinyl]amino]-1-[(2S)-4-methyl-2-[(benzyloxycarbonyl)amino]pentyl]-pyrrolidine

15

Following the procedure of Example 30(e), except substituting 5-chlorobenzofuran-2-carboxylic acid, the title compound was prepared: MS (ES+) (MH+) 611.4.

Example 42

20

Preparation of (3R)-[[N^α-(7-methoxybenzofuran-2-carbonyl)-L-leucinyl]amino]-1-[(2S)-4-methyl-2-[(benzyloxycarbonyl)amino]pentyl]-pyrrolidine

Following the procedure of Example 30(e), except substituting 7-methoxybenzofuran-2-carboxylic acid, the title compound was prepared: MS (ES+) (MH+) 607.4.

25

Example 43

Preparation of (3R)-[[N^α-(3-chlorobenzo[b]thiophene-2-carbonyl)-L-leucinyl]amino]-1-[(2S)-4-methyl-2-[(benzyloxycarbonyl)amino]pentyl]-pyrrolidine

30

Following the procedure of Example 30(e), except substituting 3-chlorobenzo[b]thiophene-2-carboxylic acid, the title compound was prepared: MS (ES+) (MH+) 627.3.

Example 44Preparation of (3R)-[[N^α-(3-(2-pyridyl)benzoyl)-L-leucinyl]amino]-1-[(2S)-4-methyl-2-[(benzyloxycarbonyl)amino]pentyl]-pyrrolidine

5

Following the procedure of Example 30(e), except substituting 3-(2-pyridyl)benzoic acid, the title compound was prepared: MS (ES+) (MH+) 614.4.

Example 45

10

Preparation of (3S)-[[N^α-(benzo[b]thiophene-2-carbonyl)-L-leucinyl]amino]-1-[(2S)-4-methyl-2-[(benzyloxycarbonyl)amino]pentyl]-pyrrolidine

15

a) (3S)-[[N^α-(*tert*-butoxycarbonyl)amino]-1-[(2S)-4-methyl-2-[(benzyloxycarbonyl)amino]pentyl]-pyrrolidine

Following the procedure of Example 30(a), except substituting (3S)-(--)3-(*tert*-butoxycarbonylamino)pyrrolidine, the title compound was prepared: MS (ES+) (MH+) 420.

b) (3S)-amino-1-[(2S)-4-methyl-2-[(benzyloxycarbonyl)amino]pentyl]-pyrrolidine

20 dihydrochloride

Following the procedure of Example 30(b), except substituting the compound of Example 45(a), the title compound was prepared: MS (ES+) (MH+) 320.

c) (3S)-[[N^α-(*tert*-butoxycarbonyl)-L-leucinyl]amino]-1-[(2S)-4-methyl-2-[(benzyloxycarbonyl)amino]pentyl]-pyrrolidine

Following the procedure of Example 30(c), except substituting the compound of Example 45 (b), the title compound was prepared: MS (ES+) (MH+) 533.5.

d) (3S)-[[N^α-L-leucinyl]amino]-1-[(2S)-4-methyl-2-[(benzyloxycarbonyl)amino]pentyl]-pyrrolidine dihydrochloride

Following the procedure of Example 30(d), except substituting the compound of Example 45 (c), the title compound was prepared: MS (ES+) (MH+) 433.3.

e) (3S)-[[N^α-(benzo[b]thiophene-2-carbonyl)-L-leucinyl]amino]-1-[(2S)-4-methyl-2-[(benzyloxycarbonyl)amino]pentyl]-pyrrolidine

Following the procedure of Example 30(e), except substituting the compound of Example 45 (d), the title compound was prepared: MS (ES+) (MH+) 593.4.

Example 46

- 5 Preparation of (3S)-[N^α-(3,4-dimethoxybenzoyl)-L-leucinyl]amino]-1-[(2S)-4-methyl-2-[{(benzyloxycarbonyl)amino]pentyl}-pyrrolidine

Following the procedure of Example 45(e), except substituting 3,4-dimethoxybenzoic acid, the title compound was prepared: MS (ES+) (MH+) 597.5.

- 10 Example 47

- Preparation of (3S)-[N^α-(benzofuran-2-carbonyl)-L-leucinyl]amino]-1-[(2S)-4-methyl-2-[{(benzyloxycarbonyl)amino]pentyl}-pyrrolidine

15 Following the procedure of Example 45(e), except substituting benzofuran-2-carboxylic acid, the title compound was prepared: MS (ES+) (MH+) 577.4.

Example 48

- 20 Preparation of (3S)-[N^α-(benzothiazole-6-carbonyl)-L-leucinyl]amino]-1-[(2S)-4-methyl-2-[{(benzyloxycarbonyl)amino]pentyl}-pyrrolidine

Following the procedure of Example 45(e), except substituting benzothiazole-6-carboxylic acid, the title compound was prepared: MS (ES+) (MH+) 594.4.

- 25 Example 49

- Preparation of (3S)-[N^α-(indole-2-carbonyl)-L-leucinyl]amino]-1-[(2S)-4-methyl-2-[{(benzyloxycarbonyl)amino]pentyl}-pyrrolidine

30 Following the procedure of Example 45(e), except substituting indole-2-carboxylic acid, the title compound was prepared: MS (ES+) (MH+) 576.4.

Example 50Preparation of (3S)-[N^α-(4-fluorobenzoyl)-L-leucinyl]amino]-1-[(2S)-4-methyl-2-[(benzyloxycarbonyl)amino]pentyl]-pyrrolidine

5

Following the procedure of Example 45(e), except substituting 4-fluorobenzoic acid, the title compound was prepared: MS (ES+) (MH+) 555.3.

Example 51

10

Preparation of (3S)-[N^α-(4-methoxybenzoyl)-L-leucinyl]amino]-1-[(2S)-4-methyl-2-[(benzyloxycarbonyl)amino]pentyl]-pyrrolidine

15

Following the procedure of Example 45(e), except substituting p-4-methoxybenzoic acid, the title compound was prepared: MS (ES+) (MH+) 567.3.

Example 52

20

Preparation of (3S)-[N^α-(3,4-dichlorobenzoyl)-L-leucinyl]amino]-1-[(2S)-4-methyl-2-[(benzyloxycarbonyl)amino]pentyl]-pyrrolidine

Following the procedure of Example 45(e), except substituting 3,4-dichlorobenzoic acid, the title compound was prepared: MS (ES+) (MH+) 605.2.

25

Example 53Preparation of (3S)-[N^α-(thiophene-2-carbonyl)-L-leucinyl]amino]-1-[(2S)-4-methyl-2-[(benzyloxycarbonyl)amino]pentyl]-pyrrolidine

30

Following the procedure of Example 45(e), except substituting thiophene-3-carboxylic acid, the title compound was prepared: MS (ES+) (MH+) 543.2.

Example 54

- 5 Preparation of (3S)-[[N^α-(4-biphenylcarbonyl)-L-leucinyl]amino]-1-[(2S)-4-methyl-2-[(benzyloxycarbonyl)amino]pentyl]-pyrrolidine

Following the procedure of Example 39, except substituting the compound of Example 45 (e), the title compound was prepared: MS (ES+) (MH+) 613.4.

Example 55

- 10 Preparation of (3S)-[[N^α-(5-methoxybenzofuran-2-carbonyl)-L-leucinyl]amino]-1-[(2S)-4-methyl-2-[(benzyloxycarbonyl)amino]pentyl]-pyrrolidine

15 Following the procedure of Example 45(e), except substituting 5-methoxybenzofuran-2-carboxylic acid, the title compound was prepared: MS (ES+) (MH+) 607.4.

Example 56

- 20 Preparation of (3S)-[[N^α-(5-chlorobenzofuran-2-carbonyl)-L-leucinyl]amino]-1-[(2S)-4-methyl-2-[(benzyloxycarbonyl)amino]pentyl]-pyrrolidine

Following the procedure of Example 45(e), except substituting 5-chlorobenzofuran-2-carboxylic acid, the title compound was prepared: MS (ES+) (MH+) 611.4.

- 25 Example 57

- Preparation of (3S)-[[N^α-(7-methoxybenzofuran-2-carbonyl)-L-leucinyl]amino]-1-[(2S)-4-methyl-2-[(benzyloxycarbonyl)amino]pentyl]-pyrrolidine

30 Following the procedure of Example 45(e), except substituting 7-methoxybenzofuran-2-carboxylic acid, the title compound was prepared: MS (ES+) (MH+) 607.4.

Example 58

Preparation of (3S)-[[N^α-(3-chlorobenzo[b]thiophene-2-carbonyl)-L-leucinyl]amino]-1-[(2S)-4-methyl-2-[(benzyloxycarbonyl)amino]pentyl]-pyrrolidine

5

Following the procedure of Example 45(e), except substituting 3-chlorobenzo[b]thiophene-2-carboxylic acid, the title compound was prepared: MS (ES+) (MH+) 627.2.

10

Example 59

Preparation of (3S)-[[N^α-(3-(2-pyridyl)benzoyl)-L-leucinyl]amino]-1-[(2S)-4-methyl-2-[(benzyloxycarbonyl)amino]pentyl]-pyrrolidine

15

Following the procedure of Example 45(e), except substituting 3-(2-pyridyl)benzoic acid, the title compound was prepared: MS (ES+) (MH+) 614.4.

Example 60

20 Preparation of 1-(4-phenyl)benzyl-(3S)-[[N^α-(*tert*-butoxycarbonyl)-L-leucinyl]amino]-pyrrolidine

a) 1-(2,2,2-trichloroethylcarbonyl)-(3S)-[[N^α-(*tert*-butoxycarbonyl)amino]-pyrrolidine

To a stirred solution of (3S)-(-)-3-(*tert*-butoxycarbonylamino)pyrrolidine (10 g, 53.7 mmol) in CH₂Cl₂ (150 mL) at 0°C was added N-methylmorpholine (6.50 mL, 59.1 mmol), and 2,2,2-trichloroethyl chloroformate (8.20 mL, 59.6 mmol). After stirring overnight, gradually warming to room temperature, the reaction mixture was concentrated to 1/2 original volume, diluted with CHCl₃ (250 mL), and washed with 5% NaHCO₃, H₂O, 1N HCl, H₂O, and brine, then dried (MgSO₄), filtered, and concentrated to give 23.98 g of the title compound: ¹H-NMR (400 MHz, CDCl₃): d (ppm) 4.74 (s, 2H); 4.66 (br m, 1H); 4.25 (br m, 1H); 3.72 (m, 1H); 3.56 (m, 2H); 3.33 (m, 1H); 2.19 (m, 1H); 1.87 (m, 1H); 1.45 (s, 9H).

b) 1-(2,2,2-trichloroethylcarbonyl)-(3S)-[[N^α-(*tert*-butoxycarbonyl)-L-leucinyl]amino]-pyrrolidine

35 The compound of Example 60(a) (23.9 g) was dissolved in 4.0 N HCl in dioxane (200 mL) and stirred at room temperature for 1 h. The solution was concentrated to a white solid and stored under high vacuum for 30 min. To a stirred solution of the residue in DMF (200 mL) was

added N-methylmorpholine (8.90 mL, 80.9 mmol), HOBr (10.88 g, 80.5 mmol), Boc-Leucine hydrate (20.09 g, 80.6 mmol), and EDC (15.44 g, 80.6 mmol). The reaction was stirred overnight whereupon it was partitioned between EtOAc (300 mL), 10% Na₂CO₃ (150 mL), and brine (150 mL). The aqueous layer was washed with fresh EtOAc (100 mL), the combined
5 organic layers were washed with 1N HCl, H₂O, 10% Na₂CO₃, H₂O, and brine, then dried (MgSO₄), filtered, and concentrated to give 27.88 g of the title compound: MS (ES+) (MH+) 474.1.

c) (3S)-[[N^α-(*tert*-butoxycarbonyl)-L-leucinyl]amino]-pyrrolidine

10 To a stirred solution of the compound of Example 60(b) (27.7 g) in THF (200 mL) was added a solution of 1N NH₄OAc (pH 7-7.5, 40 mL), followed by Zn powder (25.06 g). The reaction was stirred for 3 h at room temperature whereupon the slurry was filtered through a pad of Celite, followed by several CHCl₃ washes. The combined filtrates were concentrated to remove THF, diluted with additional CHCl₃ (300 mL) and washed with 10% Na₂CO₃ and
15 brine, then dried (MgSO₄), filtered, and concentrated to give 16.34 g of the title compound: MS (ES+) (MH+) 300.2.

d) 1-(4-phenyl)benzyl-(3S)-[[N^α-(*tert*-butoxycarbonyl)-L-leucinyl]amino]-pyrrolidine

20 To a stirred solution of the compound of Example 60(c) (1.51 g, 5.0 mmol) in CH₂Cl₂ (10 mL) was added 4,4'-biphenylcarbaldehyde (1.09 g, 6.0 mmol). The reaction was stirred 2 h whereupon Na(OAc)₃ (2.34 g, 11.0 mmol) was added. After stirring overnight, the reaction mixture was diluted with CHCl₃ (100 mL) and washed with 5% NaHCO₃ and brine, then dried (MgSO₄), filtered, and concentrated. Column chromatography (silica gel, 2:1 EtOAc: hexane to 3:1 EtOAc: hexane) gave 1.68 g of the title compound: MS (ES+) (MH+) 466.4.
25

Example 61

Preparation of 1-(4-phenyl)benzyl-(3S)-[[N^α-(2-naphthylcarbonyl)-L-leucinyl]amino]-pyrrolidine

30 a) 1-(4-phenyl)benzyl-(3S)-[[N^α-L-leucinyl]amino]-pyrrolidine dihydrochloride
The compound of Example 60(d) (1.57 g, 3.4 mmol) was dissolved in 4.0 N HCl in dioxane (25 mL) and stirred at room temperature for 1 h. The solution was concentrated to a white solid and dried under high vacuum for 30 min to give the title compound: MS (ES+) (MH+) 366.4.
35

b) 1-(4-phenyl)benzyl-(3S)-[[N^α-(2-naphthylcarbonyl)-L-leucinyl]amino]-pyrrolidine

To a stirred solution of the compound of Example 61(a) (132.9 mg, 0.30 mmol) in DMF (1 mL) was added N-methylmorpholine (100 uL, 0.91 mmol), HOBr (62.0 mg, 0.46 mmol), 2-naphthoic acid (78.4 mg, 0.46 mmol), and EDC (87.3 mg, 0.46 mmol). The reaction was stirred overnight whereupon it was partitioned between 50 mL each of EtOAc, 10% Na₂CO₃, and brine. The aqueous layer was washed with fresh EtOAc (50 mL), the combined organic layers were washed with 10% Na₂CO₃ and brine, then dried (MgSO₄), filtered, and concentrated. Column chromatography (silica gel, 2:1 EtOAc: hexane) gave 102.8 mg of the title compound: MS (ES+) (MH+) 520.3.

10

Example 62Preparation of 1-(4-phenyl)benzyl-(3S)-[[N^α-(2-quinolinecarbonyl)-L-leucinyl]amino]-pyrrolidine

15

Following the procedure of Example 61(b), except substituting 2-quinolinecarboxylic acid, the title compound was prepared: MS (ES+) (MH+) 521.3.

Example 6320 Preparation of 1-(4-phenyl)benzyl-(3S)-[[N^α-(3,4-dimethoxybenzoyl)-L-leucinyl]amino]-pyrrolidine25
30

Following the procedure of Example 61(b), except substituting 3,4-dimethoxybenzoic acid, the title compound was prepared: MS (ES+) (MH+) 530.3.

Example 64Preparation of 1-(4-phenyl)benzyl-(3S)-[[N^α-(benzofuran-2-carbonyl)-L-leucinyl]amino]-pyrrolidine

30

Following the procedure of Example 61(b), except substituting benzofuran-2-carboxylic acid, the title compound was prepared: MS (ES+) (MH+) 510.3.

Example 65Preparation of 1-(4-phenyl)benzyl-(3S)-[[N^α-(benzo[b]thiophene-2-carbonyl)-L-leucinyl]amino]-pyrrolidine

5

Following the procedure of Example 61(b), except substituting benzo[b]thiophene-2-carboxylic acid, the title compound was prepared: MS (ES+) (MH+) 526.4.

Example 66

10

Preparation of 1-(4-phenyl)benzyl-(3S)-[[N^α-(benzyloxycarbonyl)-L-leucinyl]amino]-pyrrolidine

To a stirred suspension of the compound of Example 61(a) (132.9 mg, 0.30 mmol) in CH₂Cl₂ (2 mL) at 0°C was added N-methylmorpholine (132 uL, 1.20 mmol), and benzyl chloroformate (53 uL, 0.36 mmol). The reaction was stirred overnight, gradually warming to room temperature, whereupon it was diluted with CHCl₃ (100 mL) and washed with 10% Na₂CO₃ and brine, then dried (MgSO₄), filtered, and concentrated. Column chromatography (silica gel, EtOAc) gave 94.0 mg of the title compound: MS (ES+) (MH+) 500.3.

20

Example 67Preparation of 1-(2-phenyl)ethyl-(3S)-[[N^α-(tert-butoxycarbonyl)-L-leucinyl]amino]-pyrrolidine

25

Following the procedure of Example 60(d), except substituting phenylacetaldehyde, the title compound was prepared: MS (ES+) (MH+) 404.4.

Example 68

30

Preparation of 1-(2-phenyl)ethyl-(3S)-[[N^α-(2-naphthylcarbonyl)-L-leucinyl]amino]-pyrrolidinea) 1-(2-phenyl)ethyl-(3S)-[[N^α-L-leucinyl]amino]-pyrrolidine dihydrochloride

The compound of Example 67 (1.13 g, 2.8 mmol) was dissolved in 4.0 N HCl in dioxane (25 mL) and stirred at room temperature for 1 h. The solution was concentrated to a white solid and dried under high vacuum for 30 min to give the title compound: MS (ES+) (MH+) 304.3.

b) 1-(2-phenyl)ethyl-(3S)-[[N^α-(2-naphthylcarbonyl)-L-leucinyl]amino]-pyrrolidine

Following the procedure of Example 61(b), except substituting the compound of Example 68(a), the title compound was prepared: MS (ES+) (MH+) 458.3.

5

Example 69

Preparation of 1-(2-phenyl)ethyl-(3S)-[[N^α-(2-quinolinecarbonyl)-L-leucinyl]amino]-pyrrolidine

10 Following the procedure of Example 68(b), except substituting 2-quinolinecarboxylic acid, the title compound was prepared: MS (ES+) (MH+) 459.5.

Example 70

15 Preparation of 1-(2-phenyl)ethyl-(3S)-[[N^α-(benzo[b]thiophene-2-carbonyl)-L-leucinyl]amino]-pyrrolidine

Following the procedure of Example 68(b), except substituting benzo[b]thiophene-2-carboxylic acid, the title compound was prepared: MS (ES+) (MH+) 464.3.

20

Example 71

Preparation of 1-(2-phenyl)ethyl-(3S)-[[N^α-(benzofuran-2-carbonyl)-L-leucinyl]amino]-pyrrolidine

25

Following the procedure of Example 68(b), except substituting benzofuran-2-carboxylic acid, the title compound was prepared: MS (ES+) (MH+) 448.3.

Example 72

30

Preparation of 1-(2-phenyl)ethyl-(3S)-[[N^α-(3-chlorobenzo[b]thiophene-2-carbonyl)-L-leucinyl]amino]-pyrrolidine

35

Following the procedure of Example 68(b), except substituting 3-chlorobenzo[b]thiophene-2-carboxylic acid, the title compound was prepared: MS (ES+) (MH+) 498.1.

Example 73Preparation of 1-(4-phenoxy)benzyl-(3S)-[[N^α-(tert-butoxycarbonyl)-L-leucinyl]amino]-pyrrolidine

5

Following the procedure of Example 60(d), except substituting 4-phenoxybenzaldehyde, the title compound was prepared: MS (ES+) (MH+) 482.4.

Example 74

10

Preparation of 1-(4-phenoxy)benzyl-(3S)-[[N^α-(2-naphthylcarbonyl)-L-leucinyl]amino]-pyrrolidine

15

a) 1-(4-phenoxy)benzyl-(3S)-[[N^α-L-leucinyl]amino]-pyrrolidine dihydrochloride
The compound of Example 73 (1.52 g, 3.2 mmol) was dissolved in 4.0 N HCl in dioxane (25 mL) and stirred at room temperature for 1 h. The solution was concentrated to a white solid and dried under high vacuum for 30 min to give the title compound: MS (ES+) (MH+) 382.4.

20

b) 1-(4-phenoxy)benzyl-(3S)-[[N^α-(2-naphthylcarbonyl)-L-leucinyl]amino]-pyrrolidine

Following the procedure of Example 61(b), except substituting the compound of Example 74(a), the title compound was prepared: MS (ES+) (MH+) 536.3.

Example 75

25

Preparation of 1-(4-phenoxy)benzyl-(3S)-[[N^α-(2-quinolinecarbonyl)-L-leucinyl]amino]-pyrrolidine

Following the procedure of Example 74(b), except substituting 2-quinolinecarboxylic acid, the title compound was prepared: MS (ES+) (MH+) 537.3.

30

Example 76Preparation of 1-(4-phenoxy)benzyl-(3S)-[[N^α-(3,4-dimethoxybenzoyl)-L-leucinyl]amino]-pyrrolidine

35

Following the procedure of Example 74(b), except substituting 3,4-dimethoxybenzoic acid, the title compound was prepared: MS (ES+) (MH+) 546.3.

Example 77

Preparation of 1-(4-phenoxy)benzyl-(3S)-[[N^α-(benzofuran-2-carbonyl)-L-leucinyl]amino]-pyrrolidine

5 Following the procedure of Example 74(b), except substituting benzofuran-2-carboxylic acid, the title compound was prepared: MS (ES+) (MH+) 526.4.

10 Example 78

Preparation of 1-(4-phenoxy)benzyl-(3S)-[[N^α-(benzo[b]thiophene-2-carbonyl)-L-leucinyl]amino]-pyrrolidine

15 Following the procedure of Example 74(b), except substituting benzo[b]thiophene-2-carboxylic acid, the title compound was prepared: MS (ES+) (MH+) 542.3.

Example 79

20 Preparation of 1-(4-fluoro)benzyl-(3S)-[[N^α-(tert-butoxycarbonyl)-L-leucinyl]amino]-pyrrolidine

Following the procedure of Example 60(d), except substituting 4-fluorobenzaldehyde, the title compound was prepared: MS (ES+) (MH+) 408.3.

25 Example 80

Preparation of 1-(4-fluoro)benzyl-(3S)-[[N^α-(2-naphthylcarbonyl)-L-leucinyl]amino]-pyrrolidine

30 a) 1-(4-fluoro)benzyl-(3S)-[[N^α-L-leucinyl]amino]-pyrrolidine dihydrochloride

The compound of Example 79 (508 mg, 1.25 mmol) was dissolved in 4.0 N HCl in dioxane (25 mL) and stirred at room temperature for 1 h. The solution was concentrated to a white solid and dried under high vacuum for 30 min to give the title compound: MS (ES+)

35 (MH+) 308.3.

b) 1-(4-fluoro)benzyl-(3S)-[[N^α-(2-naphthylcarbonyl)-L-leucinyl]amino]-pyrrolidine

Following the procedure of Example 61(b), except substituting the compound of Example 80(a), the title compound was prepared: MS (ES+) (MH+) 462.3.

5

Example 81

Preparation of 1-(4-fluoro)benzyl-(3S)-[[N^α-(benzo[b]thiophene-2-carbonyl)-L-leucinyl]amino]-pyrrolidine

10

Following the procedure of Example 80(b), except substituting benzo[b]thiophene-2-carboxylic acid, the title compound was prepared: MS (ES+) (MH+) 468.3.

Example 82

15

Preparation of 1-(4-cyano)benzyl-(3S)-[[N^α-(tert-butoxycarbonyl)-L-leucinyl]amino]-pyrrolidine

Following the procedure of Example 60(d), except substituting 4-cyanobenzaldehyde, the title compound was prepared: MS (ES+) (MH+) 415.4.

20

Example 83

Preparation of 1-(4-cyano)benzyl-(3S)-[[N^α-(2-naphthylcarbonyl)-L-leucinyl]amino]-pyrrolidine

25

a) 1-(4-cyano)benzyl-(3S)-[[N^α-L-leucinyl]amino]-pyrrolidine dihydrochloride

The compound of Example 82 (512 mg, 1.23 mmol) was dissolved in 4.0 N HCl in dioxane (25 mL) and stirred at room temperature for 1 h. The solution was concentrated to a white solid and dried under high vacuum for 30 min to give the title compound: MS (ES+) (MH+) 315.4.

30

b) 1-(4-cyano)benzyl-(3S)-[[N^α-(2-naphthylcarbonyl)-L-leucinyl]amino]-pyrrolidine

Following the procedure of Example 61(b), except substituting the compound of Example 83(a), the title compound was prepared: MS (ES+) (MH+) 469.5.

35

Example 84Preparation of 1-benzyl-(3S)-[[N^α-(benzo[b]thiophene-2-carbonyl)-L-leucinyl]amino]-pyrrolidine

5

a) 1-benzyl-(3S)-[[N^α-(*tert*-butoxycarbonyl)amino]pyrrolidine

To a stirred solution of (3S)-(−)-3-(*tert*-butoxycarbonylamino)pyrrolidine (10 g, 53.7 mmol) in CH₂Cl₂ (125 mL) was added benzaldehyde (6.6 mL, 64.9 mmol). The reaction was stirred 2 h whereupon Na(OAc)₃ (25.05 g, 118.2 mmol) was added. After stirring overnight, small aliquots of 5% NaHCO₃ were added until foaming had ceased. The reaction mixture was diluted with CHCl₃ (150 mL) and washed with 5% NaHCO₃ and brine, then dried (MgSO₄), filtered, and concentrated. Column chromatography (silica gel, 1:1 EtOAc: hexane) gave 11.5 g of the title compound: MS (ES+) (MH⁺) 277.2.

10

b) 1-benzyl-(3S)-[[N^α-(*tert*-butoxycarbonyl)-L-leucinyl]amino]pyrrolidine

The compound of Example 84 (a) (11.0 g, 39.8 mmol) was dissolved in 4.0 N HCl in dioxane (300 mL) and stirred at room temperature for 1 h. The solution was concentrated to a white solid and dried under high vacuum. To a stirred solution of the residue in DMF (100 mL) was added N-methylmorpholine (13.1 mL, 119.1 mmol), HOBr (8.07 g, 59.7 mmol), Boc-Leucine hydrate (14.89 g, 59.7 mmol), and EDC (11.44 g, 59.7 mmol). The reaction was stirred overnight whereupon it was diluted with EtOAc (500 mL), and washed with 1:1 10% Na₂CO₃ : brine (300 mL). The aqueous layer was washed with fresh EtOAc (150 mL), the combined organic layers were washed with 10% Na₂CO₃ and brine, then dried (MgSO₄), filtered, and concentrated. Column chromatography (silica gel, 1:2 EtOAc: hexane to 1:1 EtOAc: hexane) gave 13.5 g of the title compound: MS (ES+) (MH⁺) 390.4.

25

c) 1-benzyl-(3S)-[[N^α-L-leucinyl]amino]pyrrolidine dihydrochloride

The compound of Example 84 (b) (11.6 g, 29.8 mmol) was dissolved in 4.0 N HCl in dioxane (300 mL) and stirred at room temperature for 1 h. The solution was concentrated to a white solid and dried under high vacuum to give the title compound: MS (ES+) (MH⁺) 290.4.

30

d) 1-benzyl-(3S)-[[N^α-(benzo[b]thiophene-2-carbonyl)-L-leucinyl]amino]pyrrolidine

To a stirred solution of the compound of Example 84 (c) (109.2 mg, 0.30 mmol) in DMF (1 mL) was added N-methylmorpholine (100 uL, 0.91 mmol), HOBr (61.6 mg, 0.46 mmol), benzo[b]thiophene-2-carboxylic acid (80.8 mg, 0.45 mmol), and EDC (86.6 mg, 0.45 mmol). The reaction was stirred overnight whereupon it was partitioned between 50 mL each of EtOAc, 10% Na₂CO₃, and brine. The aqueous layer was washed with fresh EtOAc (50 mL), the

combined organic layers were washed with 10% Na₂CO₃ and brine, then dried (MgSO₄), filtered, and concentrated. Column chromatography (silica gel, 4:1 EtOAc: hexane) gave 85.0 mg of the title compound: MS (ES+) (MH+) 450.0.

5

Example 85Preparation of 1-benzyl-(3S)-[[N^α-(3,4-dimethoxybenzoyl)-L-leucinyl]amino]-pyrrolidine

Following the procedure of Example 84(d), except substituting 3,4-dimethoxybenzoic acid, the title compound was prepared: MS (ES+) (MH+) 454.4.

10
Example 86Preparation 1-benzyl-(3S)-[[N^α-(3-(2-dimethylaminoethoxy)-4-methoxybenzoyl)-L-leucinyl]amino]-pyrrolidine

Following the procedure of Example 84(d), except substituting 3-(2-dimethylaminoethoxy)-4-methoxybenzoic acid, the title compound was prepared: MS (ES+) (MH+) 511.2.

20

Example 87Preparation of 1-(4-nitro)benzyl-(3S)-[[N^α-(2-naphthylcarbonyl)-L-leucinyl]amino]-pyrrolidine25 a) 1-benzyl-(3S)-[[N^α-(2-naphthylcarbonyl)-L-leucinyl]amino]-pyrrolidine

To a stirred solution of the compound of Example 84 (c) (7.25 g, 20.0 mmol) in DMF (50 mL) was added N-methylmorpholine (6.60 mL, 60.0 mmol), HOEt (4.05 g, 30.0 mmol), 2-naphthoic acid (5.17 g, 30.0 mmol), and EDC (5.76 g, 30.1 mmol). The reaction was stirred overnight whereupon it was partitioned between EtOAc (300 mL), 10% Na₂CO₃ (150 mL), and brine (150 mL). The aqueous layer was washed with fresh EtOAc (150 mL), the combined organic layers were washed with 10% Na₂CO₃ and brine, then dried (MgSO₄), filtered, and concentrated. Column chromatography (silica gel, 3:1 EtOAc: hexane to EtOAc) gave 5.7 g of the title compound: MS (ES+) (MH+) 444.0.

30
35 b) (3S)-[[N^α-(2-naphthylcarbonyl)-L-leucinyl]amino]-pyrrolidine

To a stirred suspension of the compound of Example 87(a) (2.22 g, 5.00 mmol) in anhydrous dichloroethane (10 mL) at 0°C, in an oven-dried flask under an Argon atmosphere,

- was added a solution of 1-chloroethyl chloroformate (600 uL, 5.56 mmol) in dichloroethane, drop-wise over 10 min. After stirring at 0°C for 15 min, the reaction was heated to reflux for 1.5 h, cooled to room temperature, and concentrated. The residue was dissolved in anhydrous MeOH (10 mL) and heated to reflux overnight. The reaction was cooled to room temperature, 5 whereupon it was concentrated, dissolved in H₂O, and basified to pH 9-9.5 by the addition of solid Na₂CO₃. The aqueous solution was extracted with CHCl₃ (2 x 100 mL), the combined organic layers were washed with brine, then dried (MgSO₄), filtered, and concentrated. Column chromatography (silica gel, 10:90 MeOH: CHCl₃ to 10:90:0.1 MeOH: CHCl₃ : NH₄OH) gave 0.82 g of the title compound: MS (ES+) (MH⁺) 354.3.
- 10 c) 1-(4-nitro)benzyl-(3S)-[[N^α-(2-naphthylcarbonyl)-L-leucinyl]amino]-pyrrolidine
To a stirred solution of the compound of Example 87(b) (106.5 mg, 0.30 mmol) in CH₂Cl₂ (1 mL) was added 4-nitrobenzaldehyde (55.5 mg, 0.37 mmol). The reaction was stirred 1.5 h whereupon Na(OAc)₃ (141.3 mg, 0.67 mmol) added. After stirring overnight, the reaction 15 mixture was diluted with CHCl₃ (100 mL) and washed with 5% NaHCO₃ and brine, then dried (MgSO₄), filtered, and concentrated. Column chromatography (silica gel, EtOAc) gave 88.0 mg of the title compound: MS (ES+) (MH⁺) 489.3.

Example 88

- 20 Preparation of 1-(4-(N,N-dimethylamino)benzyl-(3S)-[[N^α-(2-naphthylcarbonyl)-L-
leucinyl]amino]-pyrrolidine

Following the procedure of Example 87(c), except substituting 4-(N,N-dimethylamino)benzaldehyde, the title compound was prepared: MS (ES+) (MH⁺) 487.1.

Example 89

- 30 Preparation of 1-(4-methoxy)benzyl-(3S)-[[N^α-(2-naphthylcarbonyl)-L-leucinyl]amino]-pyrrolidine

Following the procedure of Example 87(c), except substituting p-anisaldehyde, the title compound was prepared: MS (ES+) (MH⁺) 474.4.

Example 90Preparation of 1-(4-pyridyl)methyl-(3S)-[[N^α-(2-naphthylcarbonyl)-L-leucinyl]amino]-pyrrolidine

5

Following the procedure of Example 87(c), except substituting 4-pyridinecarboxaldehyde, the title compound was prepared: MS (ES+) (MH+) 445.4.

Example 91

10

Preparation of 1-(4-carboxymethyl)benzyl-(3S)-[[N^α-(2-naphthylcarbonyl)-L-leucinyl]amino]-pyrrolidine

15

Following the procedure of Example 87(c), except substituting methyl-4-formylbenzoate, the title compound was prepared: MS (ES+) (MH+) 502.3.

Example 92

20

Preparation of 1-(3,4-methylenedioxy)benzyl-(3S)-[[N^α-(2-naphthylcarbonyl)-L-leucinyl]amino]-pyrrolidine

Following the procedure of Example 87(c), except substituting piperonal, the title compound was prepared: MS (ES+) (MH+) 488.2.

25

Example 93Preparation of 1-(2-naphthyl)methyl-(3S)-[[N^α-(2-naphthylcarbonyl)-L-leucinyl]amino]-pyrrolidine

30

Following the procedure of Example 87(c), except substituting 2-naphthaldehyde, the title compound was prepared: MS (ES+) (MH+) 494.2.

Example 94Preparation of 1-(3-indolyl)methyl-(3S)-[[N^α-(2-naphthylcarbonyl)-L-leucinyl]amino]-pyrrolidine

5

Following the procedure of Example 87(c), except substituting indole-3-carboxaldehyde, the title compound was prepared: MS (ES+) (MH+) 483.4.

Example 95

10

Preparation of 1-(2-quinolinyl)methyl-(3S)-[[N^α-(2-naphthylcarbonyl)-L-leucinyl]amino]-pyrrolidine

15

Following the procedure of Example 87c), except substituting quinoline-2-carboxaldehyde, the title compound was prepared: MS (ES+) (MH+) 495.4.

Example 96Preparation of 1-(3-quinolinyl)methyl-(3S)-[[N^α-(2-naphthylcarbonyl)-L-leucinyl]amino]-20 pyrrolidine

Following the procedure of Example 87(c), except substituting quinoline-3-carboxaldehyde, the title compound was prepared: MS (ES+) (MH+) 495.3.

25

Example 97Preparation of 1-(1-naphthyl)methyl-(3S)-[[N^α-(2-naphthylcarbonyl)-L-leucinyl]amino]-pyrrolidine

30

Following the procedure of Example 87(c), except substituting 1-naphthaldehyde, the title compound was prepared: MS (ES+) (MH+) 494.3.

Example 98Preparation of 1-(4-quinolinyl)methyl-(3S)-[[N^α-(2-naphthylcarbonyl)-L-leucinyl]amino]-pyrrolidine

5

Following the procedure of Example 87(c), except substituting quinoline-4-carboxaldehyde, the title compound was prepared: MS (ES+) (MH+) 495.3.

Example 99

10

Preparation 1-(3-pyrrolyl)methyl-(3S)-[[N^α-(2-naphthylcarbonyl)-L-leucinyl]amino]-pyrrolidine

15

Following the procedure of Example 87(c), except substituting pyrrole-2-carboxaldehyde, the title compound was prepared: MS (ES+) (MH+) 433.3.

Example 100

20

Preparation of 1-(3-pyridyl)methyl-(3S)-[[N^α-(2-naphthylcarbonyl)-L-leucinyl]amino]-pyrrolidine

Following the procedure of Example 87(c), except substituting pyridine-3-carboxaldehyde, the title compound was prepared: MS (ES+) (MH+) 445.2.

25

Example 101Preparation of 1-(2-pyridyl)methyl-(3S)-[[N^α-(2-naphthylcarbonyl)-L-leucinyl]amino]-pyrrolidine

30

Following the procedure of Example 87(c), except substituting pyridine-2-carboxaldehyde, the title compound was prepared: MS (ES+) (MH+) 445.1.

Example 102Preparation of 1-(3-nitro)benzyl-(3S)-[[N^α-(2-naphthylcarbonyl)-L-leucinyl]amino]-pyrrolidine

5 Following the procedure of Example 87(c), except substituting 3-nitrobenzaldehyde, the title compound was prepared: MS (ES+) (MH⁺) 489.3.

Example 103

10 Preparation of 1-(4-acetamido)benzyl-(3S)-[[N^α-(2-naphthylcarbonyl)-L-leucinyl]amino]-pyrrolidine

a) 1-(2,2,2-trichloroethyl)carbonyl-(3S)-[[N^α-(*tert*-butoxycarbonyl)amino]-pyrrolidine

To a stirred solution of (3S)-(−)-3-(*tert*-butoxycarbonylamino)pyrrolidine (10 g, 53.7

15 mmol) in CH₂Cl₂ (150 mL) at 0°C was added N-methylmorpholine (6.50 mL, 59.1 mmol), and 2,2,2-trichloroethyl chloroformate (8.20 mL, 59.6 mmol). After stirring overnight, gradually warming to room temperature, the reaction mixture was diluted with CHCl₃ (250 mL) and washed with 5% NaHCO₃, H₂O, 1N HCl, H₂O, and brine, then dried (MgSO₄), filtered, and concentrated to give 19.96 g of the title compound: ¹H-NMR (400 MHz, CDCl₃): δ (ppm) 4.74 (s, 2H); 4.66 (br m, 1H); 4.25 (br m, 1H); 3.72 (m, 1H); 3.56 (m, 2H); 3.33 (m, 1H); 2.19 (m, 1H); 1.87 (m, 1H); 1.45 (s, 9H).

b) 1-(2,2,2-trichloroethyl)carbonyl-(3S)-[[N^α-(*tert*-butoxycarbonyl)-L-leucinyl]amino]-pyrrolidine

25 The compound of Example 103 (a) (19.9 g) was dissolved in 4.0 N HCl in dioxane (400 mL) and stirred at room temperature for 1 h. The solution was concentrated to a white solid and stored under high vacuum. To a stirred solution of the residue in DMF (200 mL) was added N-methylmorpholine (8.90 mL, 80.9 mmol), HOBr (10.88 g, 80.5 mmol), Boc-Leucine hydrate (20.10 g, 80.6 mmol), and EDC (15.45 g, 80.7 mmol). The reaction was stirred overnight 30 whereupon it was concentrated to remove most of the DMF, then diluted with EtOAc (300 mL), and washed with brine (150 mL). The aqueous layer was washed with fresh EtOAc (100 mL), the combined organic layers were washed with 1N HCl, H₂O, 10% Na₂CO₃, H₂O, and brine, then dried (MgSO₄), filtered, and concentrated to give 24.64 g of the title compound: ¹H-NMR (400 MHz, CDCl₃): δ (ppm) 6.55 (br m, 1H); 4.88 (m, 1H); 4.76 (s, 2H); 4.48 (m, 1H); 4.03 (m, 1H); 3.75 (m, 1H); 3.58 (m, 2H); 3.33 (m, 1H); 2.19 (m, 1H); 1.88 (m, 1H); 1.64 (m, 2H); 1.49 (m, 1H); 1.44 (s, 9H); 0.93 (m, 6H).

c) 1-(2,2,2-trichloroethyl)carbonyl-(3S)-[[N^α-L-leucinyl]amino]-pyrrolidine hydrochloride

The compound of Example 103 (b) (24.5 g) was dissolved in 4.0 N HCl in dioxane (500 mL) and stirred at room temperature for 1 h. The solution was concentrated to a white solid and dried under high vacuum to give the title compound: MS (ES+) (MH+) 375.

5

d) 1-(2,2,2-trichloroethyl)carbonyl-(3S)-[[N^α-(2-naphthylcarbonyl)-L-leucinyl]amino]-pyrrolidine

To a stirred solution of the compound of Example 103(c) (10.28 g, 25.0 mmol) in DMF (75 mL) was added N-methylmorpholine (4.2 mL, 38.2 mmol), HOBt (5.07 g, 37.5 mmol), 2-naphthoic acid (6.46 g, 37.5 mmol), and EDC (7.18 g, 37.5 mmol). The reaction was stirred overnight whereupon it was concentrated to remove most of the DMF, then partitioned between EtOAc (300 mL), 1N HCl (150 mL), and brine (150 mL). The aqueous layer was washed with fresh EtOAc (150 mL), the combined organic layers were washed with 1N HCl, H₂O, 10% Na₂CO₃, H₂O, and brine, then dried (MgSO₄), filtered, and concentrated. Column chromatography (silica gel, 1:2 EtOAc : hexane to 1:1 EtOAc : hexane) gave 9.74 g of the title compound: MS (ES+) (MH+) 528.1.

10

e) (3S)-[[N^α-(2-naphthylcarbonyl)-L-leucinyl]amino]-pyrrolidine

To a stirred solution of the compound of Example 103(d) (9.65 g) in THF (75 mL) was added a solution of 1N NH₄OAc (pH 7-7.5, 15 mL), followed by Zn powder (9.53 g). The reaction was stirred for 5 h at room temperature whereupon fresh Zn (4 g) was added and the reaction was stirred overnight. The slurry was filtered through a pad of Celite, followed by several THF washes. The combined filtrates were concentrated to remove THF, diluted with CHCl₃ (300 mL), washed with 10% Na₂CO₃ and brine, then dried (MgSO₄), filtered, and concentrated. Column chromatography (silica gel, 10:90 MeOH : CHCl₃ to 10:90:0.25 MeOH : CHCl₃ : NH₄OH) gave 5.71 g of the title compound: MS (ES+) (MH+) 354.2.

15

f) 1-(4-acetamido)benzyl-(3S)-[[N^α-(2-naphthylcarbonyl)-L-leucinyl]amino]-pyrrolidine

To a stirred solution of the compound of Example 103(e) (106.5 mg, 0.3 mmol) in CH₂Cl₂ (1 mL) was added 4-acetamidobenzaldehyde (59.7 mg, 0.37 mmol). The reaction was stirred 2 h whereupon Na(OAc)₃ (140.0 mg, 0.66 mmol) was added. After stirring overnight, the reaction mixture was diluted with CHCl₃ (100 mL) and washed with 5% NaHCO₃ and brine, then dried (MgSO₄), filtered, and concentrated. Column chromatography (silica gel, 5:95 MeOH : EtOAc) gave 105.1 mg of the title compound: MS (ES+) (MH+) 501.4.

35

Example 104Preparation of 1-(3-cyano)benzyl-(3S)-[[N^α-(2-naphthylcarbonyl)-L-leucinyl]amino]-pyrrolidine

5

Following the procedure of Example 103(f), except substituting 3-cyanobenzaldehyde, the title compound was prepared: MS (ES+) (MH+) 469.2.

Example 105

10

Preparation of 1-(3-fluoro)benzyl-(3S)-[[N^α-(2-naphthylcarbonyl)-L-leucinyl]amino]-pyrrolidine

Following the procedure of Example 103(f), except substituting 3-fluorobenzaldehyde, 15 the title compound was prepared: MS (ES+) (MH+) 462.3.

Example 106Preparation of 1-(3-phenoxy)benzyl-(3S)-[[N^α-(2-naphthylcarbonyl)-L-leucinyl]amino]-pyrrolidine

Following the procedure of Example 103(f), except substituting 3-phenoxybenzaldehyde, the title compound was prepared: MS (ES+) (MH+) 536.3.

25

Example 107Preparation of 1-(4-chloro)benzyl-(3S)-[[N^α-(2-naphthylcarbonyl)-L-leucinyl]amino]-pyrrolidine

30

Following the procedure of Example 103(f), except substituting 4-chlorobenzaldehyde, the title compound was prepared: MS (ES+) (MH+) 478.3.

Example 108Preparation of 1-(4-trifluoromethyl)benzyl-(3S)-[[N^α-(2-naphthylcarbonyl)-L-leucinyl]amino]-pyrrolidine

5

Following the procedure of Example 103(f), except substituting 4-(trifluoromethyl)benzaldehyde, the title compound was prepared: MS (ES+) (MH+) 512.3.

Example 109

10

Preparation of 1-(3-trifluoromethyl)benzyl-(3S)-[[N^α-(2-naphthylcarbonyl)-L-leucinyl]amino]-pyrrolidine

15

Following the procedure of Example 103(f), except substituting 3-(trifluoromethyl)benzaldehyde, the title compound was prepared: MS (ES+) (MH+) 512.2.

Example 110

20

Preparation of 1-(4-(3-(N,N-dimethylamino)propoxy)benzyl-(3S)-[[N^α-(2-naphthylcarbonyl)-L-leucinyl]amino]-pyrrolidine

25

Following the procedure of Example 103(f), except substituting 4-(3-dimethylaminopropoxy)benzaldehyde, the title compound was prepared: MS (ES+) (MH+) 545.2.

25

Example 111

30

Preparation of 1-(4-(isopropyl)benzyl-(3S)-[[N^α-(2-naphthylcarbonyl)-L-leucinyl]amino]-pyrrolidine

Following the procedure of Example 103(f), except substituting 4-isopropylbenzaldehyde, the title compound was prepared: MS (ES+) (MH+) 486.4.

Example 112Preparation of 1-(2-benzofuranyl)methyl-(3S)-[[N^α-(2-naphthylcarbonyl)-L-leucinyl]amino]-pyrrolidine

5

Following the procedure of Example 103(f), except substituting benzofuran-2-carboxaldehyde, the title compound was prepared: MS (ES+) (MH+) 484.2.

Example 113

10

Preparation of 1-(2-(3-methylbenzo[b]thiophenyl)methyl-(3S)-[[N^α-(2-naphthylcarbonyl)-L-leucinyl]amino]-pyrrolidine

15

Following the procedure of Example 103(f), except substituting 3-methylbenzo[b]thiophene-2-carboxaldehyde, the title compound was prepared: MS (ES+) (MH+) 514.2.

Example 114

20

Preparation of 1-(2-furanyl)methyl-(3S)-[[N^α-(2-naphthylcarbonyl)-L-leucinyl]amino]-pyrrolidine

25

Following the procedure of Example 103(f), except substituting furan-2-carboxaldehyde, the title compound was prepared: MS (ES+) (MH+) 434.1.

25

Example 115Preparation of 1-(3-furanyl)methyl-(3S)-[[N^α-(2-naphthylcarbonyl)-L-leucinyl]amino]-pyrrolidine

30

Following the procedure of Example 103(f), except substituting furan-3-carboxaldehyde, the title compound was prepared: MS (ES+) (MH+) 434.3.

Example 116Preparation of SB 1-(2-thiophenyl)methyl-(3S)-[[N^α-(2-naphthylcarbonyl)-L-leucinyl]amino]-pyrrolidine

5

Following the procedure of Example 103(f), except substituting thiophene-3-carboxaldehyde, the title compound was prepared: MS (ES+) (MH+) 450.3.

Example 117

10

Preparation of 1-(2-nitro)benzyl-(3S)-[[N^α-(2-naphthylcarbonyl)-L-leucinyl]amino]-pyrrolidine

Following the procedure of Example 103(f), except substituting 2-nitrobenzaldehyde, the title compound was prepared: MS (ES+) (MH+) 489.3.

15

Example 118Preparation of 1-(3-thiophenyl)methyl-(3S)-[[N^α-(2-naphthylcarbonyl)-L-leucinyl]amino]-pyrrolidine

20

Following the procedure of Example 103(f), except substituting thiophene-2-carboxaldehyde, the title compound was prepared: MS (ES+) (MH+) 450.2.

25

Example 119Preparation of 1-(3,4-dimethoxy)benzyl-(3S)-[[N^α-(2-naphthylcarbonyl)-L-leucinyl]amino]-pyrrolidine

30

Following the procedure of Example 103(f), except substituting 3,4-dimethoxybenzaldehyde, the title compound was prepared: MS (ES+) (MH+) 504.2.

Example 120Preparation of 1-(5-nitro-3-furanyl)methyl-(3S)-[[N^α-(2-naphthylcarbonyl)-L-leucinyl]amino]pyrrolidine

5

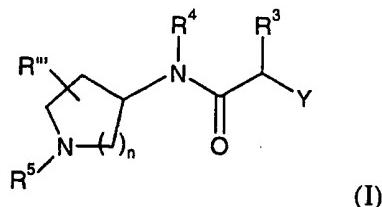
Following the procedure of Example 103(f), except substituting 5-nitrofuran-2-carboxaldehyde, the title compound was prepared: MS (ES+) (MH⁺) 479.1.

The above specification and Examples fully disclose how to make and use the
10 compounds of the present invention. However, the present invention is not limited to
the particular embodiments described hereinabove, but includes all modifications
thereof within the scope of the following claims. The various references to journals,
patents and other publications which are cited herein comprise the state of the art and
are incorporated herein by reference as though fully set forth.

15

What is claimed is:

1. A compound according to formula (I):



5

wherein:

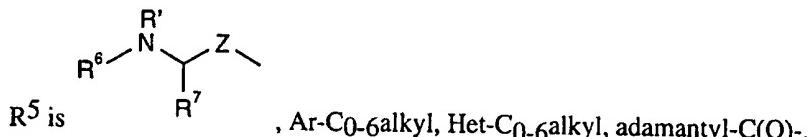
Y is Ar or NR¹R²;

R¹ is R'', R''C(O), R''C(S), R''SO₂, R''OC(O), R''R'NC(O), or R''R'NC(S);

R² is H, C₁₋₆alkyl, C₂₋₆alkenyl, Ar-C₀₋₆alkyl, or Het-C₀₋₆alkyl;

10 R³ is H, C₂₋₆alkenyl, C₂₋₆alkynyl, Het, Ar or C₁₋₆alkyl optionally substituted by OR', SR', NR'₂, N(R')C(O)OR'', CO₂R', CO₂NR'₂, N(C=NH)NH₂, Het or Ar;

R⁴ is H, C₁₋₆alkyl, C₂₋₆alkenyl, Ar-C₀₋₆alkyl, or Het-C₀₋₆alkyl;



15 Ar-C(O)-, or Het-C(O)-;

R⁶ is R'', R''C(O), R''C(S), R''SO₂, R''OC(O), R''R'NC(O), R''R'NC(S), or R''OC(O)NR'CH(R*)C(O);

R⁷ is C₃₋₆cycloalkyl-C₀₋₆alkyl, Ar-C₀₋₆alkyl, Het-C₀₋₆alkyl, Ar-C₀₋₆alkoxy, Het-C₀₋₆alkoxy, or C₁₋₆alkyl optionally substituted by OR', SR', NR'₂, N(R')C(O)OR'',

20 CO₂R', CO₂NR'₂, N(C=NH)NH₂, Het or Ar;

R* is H, C₁₋₆alkyl, C₂₋₆alkenyl, C₃₋₆cycloalkyl-C₀₋₆alkyl, Ar-C₀₋₆alkyl, Het-C₀₋₆alkyl;

each R' independently is H, C₁₋₆alkyl, C₂₋₆alkenyl, Ar-C₀₋₆alkyl, or Het-C₀₋₆alkyl;

25 each R'' independently is C₁₋₆alkyl, C₃₋₆cycloalkyl-C₀₋₆alkyl, Ar-C₀₋₆alkyl, or Het-C₀₋₆alkyl;

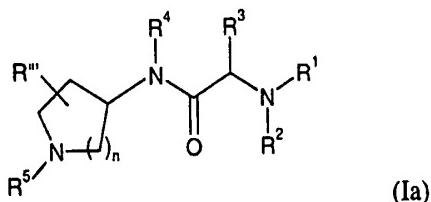
R''' is H, C₁₋₆alkyl, C₃₋₆cycloalkyl-C₀₋₆alkyl, Ar-C₀₋₆alkyl, or Het-C₀₋₆alkyl;

Z is C(O) or CH₂; and

n is 1, 2 or 3;

30 or a pharmaceutically acceptable salt thereof.

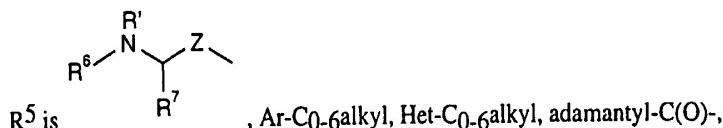
2. A compound according to formula (Ia):



wherein:

- 5 R^1 is R'' , $R''C(O)$, $R''C(S)$, $R''SO_2$, $R''OC(O)$, $R''R'NC(O)$, or $R''R'NC(S)$;
- R^2 is H, C₁₋₆alkyl, C₂₋₆alkenyl, Ar-C₀₋₆alkyl, or Het-C₀₋₆alkyl;
- R^3 is H, C₂₋₆alkenyl, C₂₋₆alkynyl, Het, Ar or C₁₋₆alkyl optionally substituted by OR', SR', NR'₂, N(R')C(O)OR'', CO₂R', CO₂NR'₂, N(C=NH)NH₂, Het or Ar;
- R^4 is H, C₁₋₆alkyl, C₂₋₆alkenyl, Ar-C₀₋₆alkyl, or Het-C₀₋₆alkyl;

10



Ar-C(O)-, or Het-C(O)-;

15 R^6 is R'' , $R''C(O)$, $R''C(S)$, $R''SO_2$, $R''OC(O)$, $R''R'NC(O)$, $R''R'NC(S)$, or
 $R''OC(O)NR'CH(R^*)C(O)$;

R^7 is C₃₋₆cycloalkyl-C₀₋₆alkyl, Ar-C₀₋₆alkyl, Het-C₀₋₆alkyl, Ar-C₀₋₆alkoxy,
 Het-C₀₋₆alkoxy, or C₁₋₆alkyl optionally substituted by OR', SR', NR'₂, N(R')C(O)OR'',
 CO₂R', CO₂NR'₂, N(C=NH)NH₂, Het or Ar;

R^* is H, C₁₋₆alkyl, C₂₋₆alkenyl, C₃₋₆cycloalkyl-C₀₋₆alkyl, Ar-C₀₋₆alkyl,

Het-C₀₋₆alkyl;20 each R' independently is H, C₁₋₆alkyl, C₂₋₆alkenyl, Ar-C₀₋₆alkyl, orHet-C₀₋₆alkyl;

each R'' independently is C₁₋₆alkyl, C₃₋₆cycloalkyl-C₀₋₆alkyl, Ar-C₀₋₆alkyl,
 or Het-C₀₋₆alkyl;

R''' is H, C₁₋₆alkyl, C₃₋₆cycloalkyl-C₀₋₆alkyl, Ar-C₀₋₆alkyl, or Het-C₀₋₆alkyl;

25 Z is C(O) or CH₂; and

n is 1, 2 or 3;

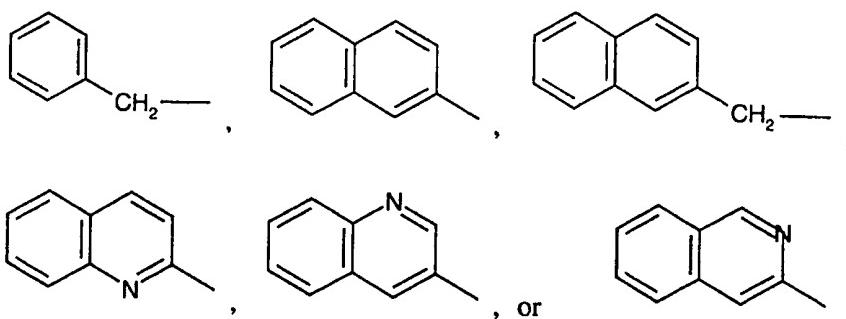
or a pharmaceutically acceptable salt thereof.

3. A compound according to claim 1 wherein R^4 and R'' are each H.

30

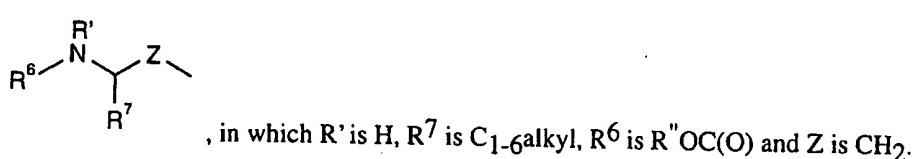
4. A compound according to claim 1 wherein R^3 is C₁₋₆alkyl.

5. A compound according to claim 4 wherein R³ is i-butyl.
6. A compound according to claim 1 wherein Y is NR¹R², in which R² is
5 H and R¹ is R["]C(O) or R["]OC(O), and R["] in said R¹ group is C₁₋₆alkyl, Ar-C₀₋₆alkyl or
Het-C₀₋₆alkyl.
7. A compound according to claim 6 wherein R["] in said R¹ group is
tert-butyl,
10



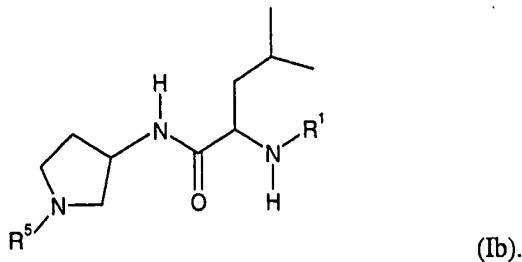
- 15 8. A compound according to claim 1 wherein n is 1 or 2.
9. A compound according to claim 8 wherein n is 1.

- 20 10. A compound according to claim 1 wherein R⁵ is benzyl or



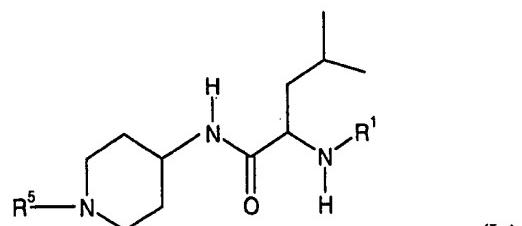
- 25 11. A compound according to claim 10 wherein, in said R⁵ group, R⁷ is i-butyl and R["] is benzyl.

12. A compound according to claim 2 of the formula (Ib):



(Ib).

13. A compound according to claim 2 of the formula (Ic):



5

(Ic).

14. A compound according to claim 1 which is:

- 3-[[N^α -(2-quinolinecarbonyl)-L-leucinyl]amino]-1-[(2S)-4-methyl-2-
 [[(benzyloxycarbonyl)amino]pentyl]-pyrrolidine;
- 10 1-benzyl-3-[[N^α -(2-quinolinecarbonyl)-L-leucinyl]amino]- pyrrolidine;
 3-[[N^α -(2-naphthylcarbonyl)-L-leucinyl]amino]-1-[(2S)-4-methyl-2-
 [[(benzyloxycarbonyl)amino]pentyl]-pyrrolidine;
 1-benzyl-3-[[N^α -(2-naphthylcarbonyl)-L-leucinyl]amino]-pyrrolidine;
 1-benzyl-(3S)-[[N^α -(benzyloxycarbonyl)-L-leucinyl]amino]-pyrrolidine;
- 15 1-benzyl-(3S)-[[N^α -(tert-butoxycarbonyl)-L-leucinyl]amino]-pyrrolidine;
 (3S)-[[N^α -(2-naphthylcarbonyl)-L-leucinyl]amino]-1-[(2S)-4-methyl-2-
 [[(benzyloxycarbonyl)amino]pentyl]-pyrrolidine;
 (3R)-[[N^α -(2-naphthylcarbonyl)-L-leucinyl]amino]-1-[(2S)-4-methyl-2-
 [[(benzyloxycarbonyl)amino]pentyl]-pyrrolidine;
- 20 1-benzyl-(3R)-[[N^α -(2-naphthyl)acetyl-L-leucinyl]amino]-pyrrolidine;
 1-benzyl-(3R)-[[N^α -(2-naphthylcarbonyl)-L-leucinyl]amino]-pyrrolidine;
 1-benzyl-(3R)-[[N^α -(3-quinolinecarbonyl)-L-leucinyl]amino]-pyrrolidine;
 1-benzyl-(3R)-[[N^α -(2-quinolinecarbonyl)-L-leucinyl]amino]-pyrrolidine;
 1-benzyl-(3R)-[[N^α -(3-isoquinolinecarbonyl)-L-leucinyl]amino]-pyrrolidine;
- 25 1-benzyl-(3S)-[[N^α -(2-naphthyl)acetyl-L-leucinyl]amino]-pyrrolidine;
 1-benzyl-(3S)-[[N^α -(2-naphthylcarbonyl)-L-leucinyl]amino]-pyrrolidine;
 1-benzyl-(3S)-[[N^α -(3-quinolinecarbonyl)-L-leucinyl]amino]-pyrrolidine;

- 1-benzyl-(3S)-[[N^α-(2-quinolinecarbonyl)-L-leucinyl]amino]-pyrrolidine;
1-benzyl-(3S)-[[N^α-(3-isoquinolinecarbonyl)-L-leucinyl]amino]-pyrrolidine;
1-benzyl-4-[[N^α-(2-naphthylcarbonyl)-L-leucinyl]amino]-piperidine;
1-benzyl-4-[[N^α-(2-quinolinecarbonyl)-L-leucinyl]amino]-piperidine;
5 1-benzyl-4-[[N^α-(benzyloxycarbonyl)-L-leucinyl]amino]-piperidine;
1-[3-(2-pyridyl)phenyl]-2-ethyl-(3S)-[[N^α-(2-naphthylcarbonyl)-L-leucinyl]amino]-pyrrolidine;
1-[3-(2-pyridyl)phenyl]-2-ethyl-(3S)-[[N^α-(2-quinolinecarbonyl)-L-leucinyl]amino]-pyrrolidine;
10 1-[3-(2-pyridyl)phenyl]-2-ethyl-(3S)-[[N^α-(3-isoquinolinecarbonyl)-L-leucinyl]amino]-pyrrolidine;
1-[3-(2-pyridyl)phenyl]-2-ethyl-(3R)-[[N^α-(2-naphthylcarbonyl)-L-leucinyl]amino]-pyrrolidine;
1-[3-(2-pyridyl)phenyl]-2-ethyl-(3R)-[[N^α-(3-isoquinolinecarbonyl)-L-leucinyl]amino]-pyrrolidine;
15 1-[3-(2-pyridyl)phenyl]-2-ethyl-(3R)-[[N^α-(2-quinolinecarbonyl)-L-leucinyl]amino]-pyrrolidine;
1-[1-adamantanecarbonyl)-(3R)-[[N^α-(4-pyridylmethoxycarbonyl)-L-leucinyl]amino]-pyrrolidine;
20 1-(1-adamantanecarbonyl)-(3S)-[[N^α-(4-pyridylmethoxycarbonyl)-L-leucinyl]amino]-pyrrolidine;
(3R)-[[N^α-(benzo[b]thiophene-2-carbonyl)-L-leucinyl]amino]-1-[(2S)-4-methyl-2-
[[benzyloxycarbonyl]amino]pentyl]-pyrrolidine;
(3R)-[[N^α-(3,4-dimethoxybenzoyl)-L-leucinyl]amino]-1-[(2S)-4-methyl-2-
25 [[benzyloxycarbonyl]amino]pentyl]-pyrrolidine;
(3R)-[[N^α-(benzofuran-2-carbonyl)-L-leucinyl]amino]-1-[(2S)-4-methyl-2-
[[benzyloxycarbonyl]amino]pentyl]-pyrrolidine;
(3R)-[[N^α-(benzothiazole-6-carbonyl)-L-leucinyl]amino]-1-[(2S)-4-methyl-2-
[[benzyloxycarbonyl]amino]pentyl]-pyrrolidine;
30 (3R)-[[N^α-(indole-2-carbonyl)-L-leucinyl]amino]-1-[(2S)-4-methyl-2-
[[benzyloxycarbonyl]amino]pentyl]-pyrrolidine;
(3R)-[[N^α-(4-fluorobenzoyl)-L-leucinyl]amino]-1-[(2S)-4-methyl-2-
[[benzyloxycarbonyl]amino]pentyl]-pyrrolidine;
(3R)-[[N^α-(4-methoxybenzoyl)-L-leucinyl]amino]-1-[(2S)-4-methyl-2-
35 [[benzyloxycarbonyl]amino]pentyl]-pyrrolidine;
(3R)-[[N^α-(3,4-dichlorobenzoyl)-L-leucinyl]amino]-1-[(2S)-4-methyl-2-
[[benzyloxycarbonyl]amino]pentyl]-pyrrolidine;

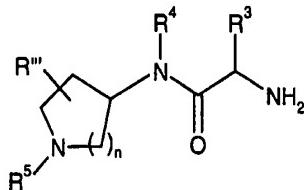
- (3R)-[[N^α-(thiophene-2-carbonyl)-L-leucinyl]amino]-1-[(2S)-4-methyl-2-
[[benzyloxycarbonyl]amino]pentyl]-pyrrolidine;
- (3R)-[[N^α-(4-biphenylcarbonyl)-L-leucinyl]amino]-1-[(2S)-4-methyl-2-
[[benzyloxycarbonyl]amino]pentyl]-pyrrolidine;
- 5 (3R)-[[N^α-(5-methoxybenzofuran-2-carbonyl)-L-leucinyl]amino]-1-[(2S)-4-methyl-2-
[[benzyloxycarbonyl]amino]pentyl]-pyrrolidine;
- (3R)-[[N^α-(5-chlorobenzofuran-2-carbonyl)-L-leucinyl]amino]-1-[(2S)-4-methyl-2-
[[benzyloxycarbonyl]amino]pentyl]-pyrrolidine;
- (3R)-[[N^α-(7-methoxybenzofuran-2-carbonyl)-L-leucinyl]amino]-1-[(2S)-4-methyl-2-
10 [[benzyloxycarbonyl]amino]pentyl]-pyrrolidine;
- (3R)-[[N^α-(3-chlorobenzo[b]thiophene-2-carbonyl)-L-leucinyl]amino]-1-[(2S)-4-methyl-2-
2-[[benzyloxycarbonyl]amino]pentyl]-pyrrolidine;
- (3R)-[[N^α-(3-(2-pyridyl)benzoyl)-L-leucinyl]amino]-1-[(2S)-4-methyl-2-
[[benzyloxycarbonyl]amino]pentyl]-pyrrolidine;
- 15 (3S)-[[N^α-(benzo[b]thiophene-2-carbonyl)-L-leucinyl]amino]-1-[(2S)-4-methyl-2-
[[benzyloxycarbonyl]amino]pentyl]-pyrrolidine;
- (3S)-[[N^α-(3,4-dimethoxybenzoyl)-L-leucinyl]amino]-1-[(2S)-4-methyl-2-
[[benzyloxycarbonyl]amino]pentyl]-pyrrolidine;
- (3S)-[[N^α-(benzofuran-2-carbonyl)-L-leucinyl]amino]-1-[(2S)-4-methyl-2-
20 [[benzyloxycarbonyl]amino]pentyl]-pyrrolidine;
- (3S)-[[N^α-(benzothiazole-6-carbonyl)-L-leucinyl]amino]-1-[(2S)-4-methyl-2-
[[benzyloxycarbonyl]amino]pentyl]-pyrrolidine;
- (3S)-[[N^α-(indole-2-carbonyl)-L-leucinyl]amino]-1-[(2S)-4-methyl-2-
[[benzyloxycarbonyl]amino]pentyl]-pyrrolidine;
- 25 (3S)-[[N^α-(4-fluorobenzoyl)-L-leucinyl]amino]-1-[(2S)-4-methyl-2-
[[benzyloxycarbonyl]amino]pentyl]-pyrrolidine;
- (3S)-[[N^α-(4-methoxybenzoyl)-L-leucinyl]amino]-1-[(2S)-4-methyl-2-
[[benzyloxycarbonyl]amino]pentyl]-pyrrolidine;
- (3S)-[[N^α-(3,4-dichlorobenzoyl)-L-leucinyl]amino]-1-[(2S)-4-methyl-2-
30 [[benzyloxycarbonyl]amino]pentyl]-pyrrolidine;
- (3S)-[[N^α-(thiophene-2-carbonyl)-L-leucinyl]amino]-1-[(2S)-4-methyl-2-
[[benzyloxycarbonyl]amino]pentyl]-pyrrolidine;
- (3S)-[[N^α-(4-biphenylcarbonyl)-L-leucinyl]amino]-1-[(2S)-4-methyl-2-
[[benzyloxycarbonyl]amino]pentyl]-pyrrolidine;
- 35 (3S)-[[N^α-(5-methoxybenzofuran-2-carbonyl)-L-leucinyl]amino]-1-[(2S)-4-methyl-2-
[[benzyloxycarbonyl]amino]pentyl]-pyrrolidine;

- (3S)-[[N^α-(5-chlorobenzofuran-2-carbonyl)-L-leucinyl]amino]-1-[(2S)-4-methyl-2-
[[(benzyloxycarbonyl)amino]pentyl]-pyrrolidine;
- (3S)-[[N^α-(7-methoxybenzofuran-2-carbonyl)-L-leucinyl]amino]-1-[(2S)-4-methyl-2-
[[(benzyloxycarbonyl)amino]pentyl]-pyrrolidine;
- 5 (3S)-[[N^α-(3-chlorobenzo[b]thiophene-2-carbonyl)-L-leucinyl]amino]-1-[(2S)-4-methyl-2-
[[(benzyloxycarbonyl)amino]pentyl]-pyrrolidine;
- (3S)-[[N^α-(3-(2-pyridyl)benzoyl)-L-leucinyl]amino]-1-[(2S)-4-methyl-2-
[[(benzyloxycarbonyl)amino]pentyl]-pyrrolidine;
- 10 1-(4-phenyl)benzyl-(3S)-[[N^α-(tert-butoxycarbonyl)-L-leucinyl]amino]-pyrrolidine;
- 1-(4-phenyl)benzyl-(3S)-[[N^α-(2-naphthylcarbonyl)-L-leucinyl]amino]-pyrrolidine;
- 1-(4-phenyl)benzyl-(3S)-[[N^α-(2-quinolinecarbonyl)-L-leucinyl]amino]-pyrrolidine;
- 1-(4-phenyl)benzyl-(3S)-[[N^α-(3,4-dimethoxybenzoyl)-L-leucinyl]amino]-pyrrolidine;
- 1-(4-phenyl)benzyl-(3S)-[[N^α-(benzofuran-2-carbonyl)-L-leucinyl]amino]-pyrrolidine;
- 1-(4-phenyl)benzyl-(3S)-[[N^α-(benzo[b]thiophene-2-carbonyl)-L-leucinyl]amino]-
15 pyrrolidine;
- 1-(4-phenyl)benzyl-(3S)-[[N^α-(benzyloxycarbonyl)-L-leucinyl]amino]-pyrrolidine;
- 1-(2-phenyl)ethyl-(3S)-[[N^α-(tert-butoxycarbonyl)-L-leucinyl]amino]-pyrrolidine;
- 1-(2-phenyl)ethyl-(3S)-[[N^α-(2-naphthylcarbonyl)-L-leucinyl]amino]-pyrrolidine;
- 1-(2-phenyl)ethyl-(3S)-[[N^α-(2-quinolinecarbonyl)-L-leucinyl]amino]-pyrrolidine;
- 20 1-(2-phenyl)ethyl-(3S)-[[N^α-(benzo[b]thiophene-2-carbonyl)-L-leucinyl]amino]-
pyrrolidine;
- 1-(2-phenyl)ethyl-(3S)-[[N^α-(benzofuran-2-carbonyl)-L-leucinyl]amino]-pyrrolidine;
- 1-(2-phenyl)ethyl-(3S)-[[N^α-(3-chlorobenzo[b]thiophene-2-carbonyl)-L-leucinyl]amino]-
pyrrolidine;
- 25 1-(4-phenoxy)benzyl-(3S)-[[N^α-(tert-butoxycarbonyl)-L-leucinyl]amino]-pyrrolidine;
- 1-(4-phenoxy)benzyl-(3S)-[[N^α-(2-naphthylcarbonyl)-L-leucinyl]amino]-pyrrolidine;
- 1-(4-phenoxy)benzyl-(3S)-[[N^α-(2-quinolinecarbonyl)-L-leucinyl]amino]-pyrrolidine;
- 1-(4-phenoxy)benzyl-(3S)-[[N^α-(3,4-dimethoxybenzoyl)-L-leucinyl]amino]-pyrrolidine;
- 1-(4-phenoxy)benzyl-(3S)-[[N^α-(benzofuran-2-carbonyl)-L-leucinyl]amino]-pyrrolidine
- 30 1-(4-phenoxy)benzyl-(3S)-[[N^α-(benzo[b]thiophene-2-carbonyl)-L-leucinyl]amino]-
pyrrolidine;
- 1-(4-fluoro)benzyl-(3S)-[[N^α-(tert-butoxycarbonyl)-L-leucinyl]amino]-pyrrolidine;
- 1-(4-fluoro)benzyl-(3S)-[[N^α-(2-naphthylcarbonyl)-L-leucinyl]amino]-pyrrolidine;
- 1-(4-fluoro)benzyl-(3S)-[[N^α-(benzo[b]thiophene-2-carbonyl)-L-leucinyl]amino]-
35 pyrrolidine;
- 1-(4-cyano)benzyl-(3S)-[[N^α-(tert-butoxycarbonyl)-L-leucinyl]amino]-pyrrolidine;
- 1-(4-cyano)benzyl-(3S)-[[N^α-(2-naphthylcarbonyl)-L-leucinyl]amino]-pyrrolidine;

- 1-benzyl-(3S)-[[N^α-(benzo[b]thiophene-2-carbonyl)-L-leucinyl]amino]-pyrrolidine;
1-benzyl-(3S)-[[N^α-(3,4-dimethoxybenzoyl)-L-leucinyl]amino]-pyrrolidine;
1-benzyl-(3S)-[[N^α-(3-(2-dimethylaminoethoxy)-4-methoxybenzoyl)-L-leucinyl]amino]-
pyrrolidine;
- 5 1-(4-nitro)benzyl-(3S)-[[N^α-(2-naphthylcarbonyl)-L-leucinyl]amino]-pyrrolidine;
1-(4-(N,N-dimethylamino)benzyl-(3S)-[[N^α-(2-naphthylcarbonyl)-L-leucinyl]amino]-
pyrrolidine;
1-(4-methoxy)benzyl-(3S)-[[N^α-(2-naphthylcarbonyl)-L-leucinyl]amino]-pyrrolidine;
1-(4-pyridyl)methyl-(3S)-[[N^α-(2-naphthylcarbonyl)-L-leucinyl]amino]-pyrrolidine;
- 10 1-(4-carboxymethyl)benzyl-(3S)-[[N^α-(2-naphthylcarbonyl)-L-leucinyl]amino]-
pyrrolidine;
1-(3,4-methylenedioxy)benzyl-(3S)-[[N^α-(2-naphthylcarbonyl)-L-leucinyl]amino]-
pyrrolidine;
1-(2-naphthyl)methyl-(3S)-[[N^α-(2-naphthylcarbonyl)-L-leucinyl]amino]-pyrrolidine;
- 15 1-(3-indolyl)methyl-(3S)-[[N^α-(2-naphthylcarbonyl)-L-leucinyl]amino]-pyrrolidine;
1-(2-quinolinyl)methyl-(3S)-[[N^α-(2-naphthylcarbonyl)-L-leucinyl]amino]-pyrrolidine;
1-(3-quinolinyl)methyl-(3S)-[[N^α-(2-naphthylcarbonyl)-L-leucinyl]amino]-pyrrolidine;
1-(1-naphthyl)methyl-(3S)-[[N^α-(2-naphthylcarbonyl)-L-leucinyl]amino]-pyrrolidine;
1-(4-quinolinyl)methyl-(3S)-[[N^α-(2-naphthylcarbonyl)-L-leucinyl]amino]-pyrrolidine;
- 20 1-(3-pyrrolyl)methyl-(3S)-[[N^α-(2-naphthylcarbonyl)-L-leucinyl]amino]-pyrrolidine;
1-(3-pyridyl)methyl-(3S)-[[N^α-(2-naphthylcarbonyl)-L-leucinyl]amino]-pyrrolidine;
1-(2-pyridyl)methyl-(3S)-[[N^α-(2-naphthylcarbonyl)-L-leucinyl]amino]-pyrrolidine;
1-(3-nitro)benzyl-(3S)-[[N^α-(2-naphthylcarbonyl)-L-leucinyl]amino]-pyrrolidine;
1-(4-acetamido)benzyl-(3S)-[[N^α-(2-naphthylcarbonyl)-L-leucinyl]amino]-pyrrolidine;
- 25 1-(3-cyano)benzyl-(3S)-[[N^α-(2-naphthylcarbonyl)-L-leucinyl]amino]-pyrrolidine;
1-(3-fluoro)benzyl-(3S)-[[N^α-(2-naphthylcarbonyl)-L-leucinyl]amino]-pyrrolidine;
1-(3-phenoxy)benzyl-(3S)-[[N^α-(2-naphthylcarbonyl)-L-leucinyl]amino]-pyrrolidine;
1-(4-chloro)benzyl-(3S)-[[N^α-(2-naphthylcarbonyl)-L-leucinyl]amino]-pyrrolidine;
1-(4-trifluoromethyl)benzyl-(3S)-[[N^α-(2-naphthylcarbonyl)-L-leucinyl]amino]-
30 pyrrolidine;
- 1-(3-trifluoromethyl)benzyl-(3S)-[[N^α-(2-naphthylcarbonyl)-L-leucinyl]amino]-
pyrrolidine;
1-(4-(3-(N,N-dimethylamino)propoxy)benzyl-(3S)-[[N^α-(2-naphthylcarbonyl)-L-
leucinyl]amino]-pyrrolidine;
- 35 1-(4-(isopropyl)benzyl-(3S)-[[N^α-(2-naphthylcarbonyl)-L-leucinyl]amino]-pyrrolidine;
1-(2-benzofuranyl)methyl-(3S)-[[N^α-(2-naphthylcarbonyl)-L-leucinyl]amino]-pyrrolidine;

- 1-(2-(3-methylbenzo[b]thiophenyl)methyl-(3S)-[[N^α-(2-naphthylcarbonyl)-L-leucinyl]amino]-pyrrolidine;
- 1-(2-furanyl)methyl-(3S)-[[N^α-(2-naphthylcarbonyl)-L-leucinyl]amino]-pyrrolidine;
- 1-(3-furanyl)methyl-(3S)-[[N^α-(2-naphthylcarbonyl)-L-leucinyl]amino]-pyrrolidine;
- 5 1-(2-thiophenyl)methyl-(3S)-[[N^α-(2-naphthylcarbonyl)-L-leucinyl]amino]-pyrrolidine;
- 1-(2-nitro)benzyl-(3S)-[[N^α-(2-naphthylcarbonyl)-L-leucinyl]amino]-pyrrolidine;
- (3-thiophenyl)methyl-(3S)-[[N^α-(2-naphthylcarbonyl)-L-leucinyl]amino]-pyrrolidine;
- 1-(3,4-dimethoxy)benzyl-(3S)-[[N^α-(2-naphthylcarbonyl)-L-leucinyl]amino]-pyrrolidine;
- or
- 10 1-(5-nitro-3-furanyl)methyl-(3S)-[[N^α-(2-naphthylcarbonyl)-L-leucinyl]amino]-pyrrolidine;
- a pharmaceutically acceptable salt thereof.
- 15 15. A pharmaceutical composition comprising a compound according to
any one of claims 1-14 and a pharmaceutically acceptable carrier.
16. A method of inhibiting a cysteine protease which comprises
administering a compound according to claim 1.
- 20 17. A method according to claim 16 wherein the cysteine protease is
cathepsin K.
18. A method of inhibiting bone loss which comprises administering a
compound according to claim 1.
- 25 19. A method of treating osteoporosis which comprises administering a
compound according to claim 1.
20. A method of treating gingival or periodontal disease which comprises
30 administering a compound according to claim 1.
21. A method of treating a disease characterized by excessive cartilage or
matrix degradation which comprises administering a compound according to claim 1.
- 35 22. A method according to claim 21 wherein said disease is osteoarthritis or
rheumatoid arthritis.

23. A compound according to any one of claims 1 to 14 for use as a medicament.
24. The use of a compound of the formula (I) as defined in claim 1 in the manufacture of a medicament for the treatment of diseases in which inhibition of a cysteine protease is a factor.
25. The use of a compound according to claim 24 wherein the cysteine protease is cathepsin K.
- 10
26. The use of a compound of the formula (I) as defined in claim 1 in the manufacture of a medicament for the inhibition of bone loss.
27. The use of a compound of the formula (I) as defined in claim 1 in the manufacture of a medicament for the treatment of osteoporosis.
- 15
28. The use of a compound of the formula (I) as defined in claim 1 in the manufacture of a medicament for the treatment of gingival or periodontal disease.
- 20
29. The use of a compound of the formula (I) as defined in claim 1 in the manufacture of a medicament for the treatment of diseases characterized by excessive cartilage or matrix degradation.
- 30
30. The use of a compound according to claim 29 wherein the disease characterized by excessive cartilage or matrix degradation is osteoarthritis or rheumatoid arthritis.
31. A process for preparing a compound of the formula (I) as defined in claim 1, which process comprises:
- 30
- reacting a compound of the formula (II):



(II)

or a salt thereof,

wherein R'', R³, R⁴, R⁵ and n are as defined in formula (I) of claim 1, with any reactive functional groups protected, with:

5 (a) R''C(O)Cl, in which R'' is as defined in formula (I) of
claim 1; or

(b) R''C(O)OH, in which R'' is as defined in formula (I) of
claim 1, in the presence of EDC and HOBT; or

10 (c) R''C(O)H, in which R'' is as defined in formula (I) of
claim 1, followed by reduction; or

(d) R''OC(O)Cl, in which R'' is as defined in formula (I) of
claim 1, in the presence of base; or

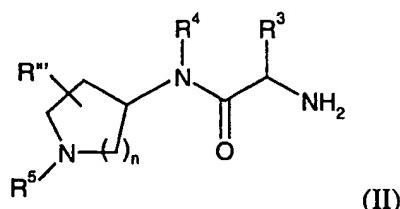
(e) R''SO₂Cl, in which R'' is as defined in formula (I) of
claim 1, in the presence of base;

15

and thereafter removing any protecting groups and optionally forming a
pharmaceutically acceptable salt.

32. A compound according to formula (II):

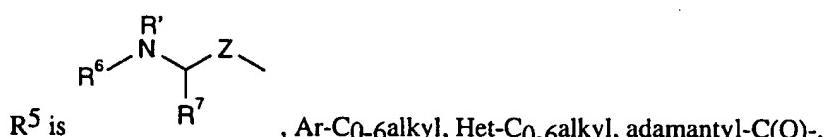
20



wherein:

R³ is H, C₂-6alkenyl, C₂-6alkynyl, Het, Ar or C₁-6alkyl optionally substituted
by OR', SR', NR'₂, N(R')C(O)OR'', CO₂R', CO₂NR'₂, N(C=NH)NH₂, Het or Ar;

25 R⁴ is H, C₁-6alkyl, C₂-6alkenyl, Ar-C₀-6alkyl, or Het-C₀-6alkyl;



Ar-C(O)-, Het-C(O)- or ;

30 R⁶ is R'', R''C(O), R''C(S), R''SO₂, R''OC(O), R''R'NC(O), R''R'NC(S), or
R''OC(O)NR'CH(R*)C(O);

R⁷ is C₃₋₆cycloalkyl-C₀₋₆alkyl, Ar-C₀₋₆alkyl, Het-C₀₋₆alkyl, Ar-C₀₋₆alkoxy, Het-C₀₋₆alkoxy, or C₁₋₆alkyl optionally substituted by OR', SR', NR'₂, N(R')C(O)OR'', CO₂R', CO₂NR'₂, N(C=NH)NH₂, Het or Ar;

R* is H, C₁₋₆alkyl, C₂₋₆alkenyl, C₃₋₆cycloalkyl-C₀₋₆alkyl, Ar-C₀₋₆alkyl.

5 Het-C₀₋₆alkyl;

each R' independently is H, C₁₋₆alkyl, C₂₋₆alkenyl, Ar-C₀₋₆alkyl, or Het-C₀₋₆alkyl;

each R'' independently is C₁₋₆alkyl, C₃₋₆cycloalkyl-C₀₋₆alkyl, Ar-C₀₋₆alkyl, or Het-C₀₋₆alkyl;

10 R''' is H, C₁₋₆alkyl, C₃₋₆cycloalkyl-C₀₋₆alkyl, Ar-C₀₋₆alkyl, or Het-C₀₋₆alkyl;

Z is C(O) or CH₂; and

n is 1, 2 or 3;

or a pharmaceutically acceptable salt thereof.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US98/09192

A. CLASSIFICATION OF SUBJECT MATTER

IPC(6) :Please See Extra Sheet.
US CL :Please See Extra Sheet.

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

U.S. : Please See Extra Sheet.

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched
NONE

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

Please See Extra Sheet.

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	US 5,514,694 A (POWERS ET AL) 07 May 1996, see entire document, especially columns 2-4.	1-32
Y	US 4,301,151 A (VEBER ET AL) 17 November 1981, see entire document, especially columns 1-4.	1-15, 31, 32
Y	US 4,680,283 A (VEBER ET AL) 14 July 1987, see entire document, especially column 8, lines 1-25.	1-15, 31, 32
A	YAMASHITA, D.S. ET AL. Structure and Design of Potent and Selective Cathepsin K Inhibitors. J. Amer. Chem. Soc. November 1997, Vol. 119, No. 46, pages 11351-11352, see entire document.	1-32



Further documents are listed in the continuation of Box C.



See patent family annex.

* Special categories of cited documents:	"T"	later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"A" document defining the general state of the art which is not considered to be of particular relevance		
"B" earlier document published on or after the international filing date	"X"	document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)	"Y"	document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"O" document referring to an oral disclosure, use, exhibition or other means		
"P" document published prior to the international filing date but later than the priority date claimed	"&"	document member of the same patent family

Date of the actual completion of the international search

18 JUNE 1998

Date of mailing of the international search report

13 AUG 1998

Name and mailing address of the ISA/US
Commissioner of Patents and Trademarks
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SUSAN HANLEY

Telephone No. (703) 308-0196

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US98/09192

C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	TSUDA, M. ET AL. Poststatin, a New Inhibitor of Prolyl Endopeptidase, VI. Endopeptidase Inhibitory Activity of Poststatin Analogues Containing Pyrrolidine Ring. J. Antibiotics. September 1996, Vol. 49, No. 9, pages 900-908, see especially page 901.	1-32
Y	TSUDA, M. ET AL. Poststatin, a New Inhibitor of Prolyl Endopeptidase, VII. N-Cycloalkylamide Analogues. J. Antibiotics. September 1996, Vol. 49, No. 9, pages 909-920, see especially pages 910-911.	1-32

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US98/09192

A. CLASSIFICATION OF SUBJECT MATTER:
IPC (6):

C12N 9/99, 9/48, 9/66, 9/50; A61K 38/00, 38/06; A01N 37/18, 43/40, 43/42, 43/36; C07D 207/00, 207/04, 207/06, 211/00, 211/08, 405/00

A. CLASSIFICATION OF SUBJECT MATTER:
US CL :

435/184, 212, 218, 219; 514/2, 277, 279, 316, 336, 408; 530/300, 323, 331, 332; 546/184, 191, 192; 548/400, 577, 579, 962

B. FIELDS SEARCHED

Minimum documentation searched

Classification System: U.S.

435/184, 212, 218, 219; 514/2, 277, 279, 316, 336, 408; 530/300, 323, 331, 332; 546/184, 191, 192; 548/400, 577, 579, 962

B. FIELDS SEARCHED

Electronic data bases consulted (Name of data base and where practicable terms used):

APS, STN, REGISTRY, BIOSIS, MEDLINE, SCISEARCH, EMBASE, CAPLUS, WPIDS
search terms: cysteine protease, cathepsin K, bone loss, arthritis